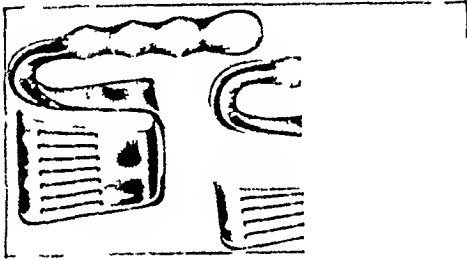


Dr. Davidson's Specialized Instruments for use in THORACOPLASTIC PROCEDURES

(By Dr Louis R Davidson, F A C S , New York City)

These improved and perfected instruments have been definitely designed to decrease operating time and promote cleaner and more technical thoracoplastic surgery Dr Davidson's refinements add to ease and comfort in manipulation while assuring a high degree of safety and efficiency in operation



Dr Davidson's RETRACTORS

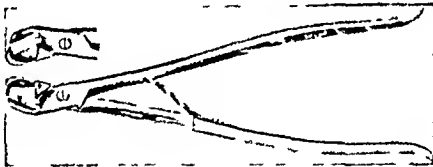
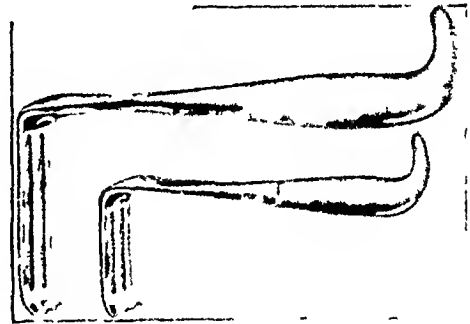
Small Blade
3" deep x 2" wide
Large or Small \$8 50 each

Retractors are definitely advanced—permit of marked retraction with little effort and prevent tiring

Dr Davidson RIB STUMP RETRACTOR

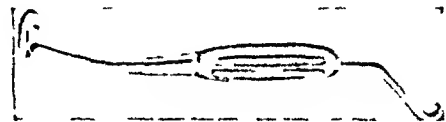
Large Blade 3 1/4" deep x 1" wide
Small Blade 2" deep x 1" wide
No 1693 Large or Small \$7 50 each

Smaller—used for all ribs except first Larger—for stump of first rib, also used to retract pectoralis muscle, thus increasing exposure of ribs anteriorly



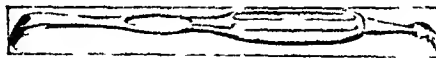
CORYLLOS RIB CUTTER

Total length 14 1/4"
Right or left
No 1698 \$22 50 each



DAVIDSON-SAUERBRUCK- DOYEN

Total length 12 1/4"
No 1696 \$16 50 each



DAVIDSON-MATHIEW-ALEXANDER-ELEVATOR

Total length 11 1/4"
No 1695 \$16 50 each

Purchase through your surgical supply house



J SKLAR MANUFACTURING CO , BROOKLYN, N. Y.

CONTENTS

Vol 106

OCTOBER, 1937

No 4

ADDRESS OF THE PRESIDENT SAMUEL GROSS
LOOKS IN ON THE AMERICAN SURGICAL AS-
SOCIATION

Evarts A Graham, M D

St Louis Mo 481

INTRACRANIAL PRESSURE WITHOUT BRAIN
TUMOR

Walter E Dandy, M D

Baltimore Md 492

THE PLACE OF EXPLORATORY OPERATION IN THE
SURGERY OF SUPPURATIVE ABSCESS

Edwin P Lehman, M D

University, Va 514

THE CONTROL OF THE HEART BEAT BY THE SUR-
GEON

Claude S Beck, M D
Frederick R Mautz, M D

Cleveland Ohio 525

SYMPOSIUM ON CANCER

FOREWORD

Evarts A Graham, M D

St Louis Mo 538

THE ETIOLOGY OF CANCER IN THE LIGHT OF OUR
PRESENT KNOWLEDGE

John J Morton, M D

Rochester N Y 539

MALIGNANT CHANGES IN THE FORESTOMACH OF
RATS

George R Sharpless, Sc D

Detroit Mich 562

OUR RESPONSIBILITY TOWARD ORAL CANCER

Vilray P Blair, M D
James Barrett Brown, M D
Louis T Byars, M D

St Louis Mo 566

EPITHELIOMA OF THE LOWER LIP

Robert H Kennedy, M D

New York 577

THE RESULTS AND METHODS OF TREATMENT OF
CANCER BY RADIATION

Professor Henri Coutard, M D

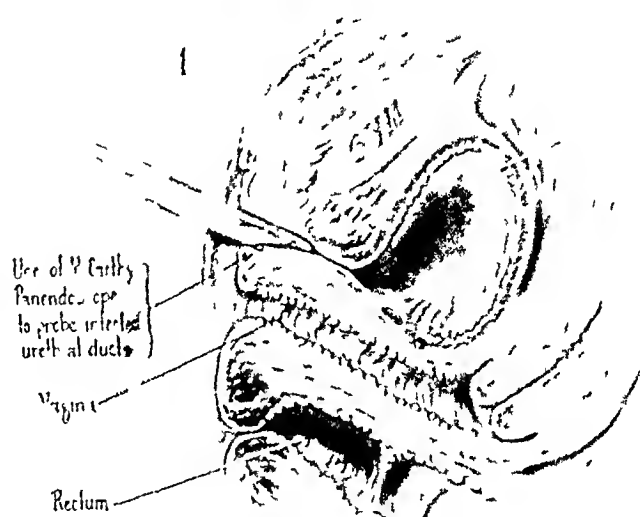
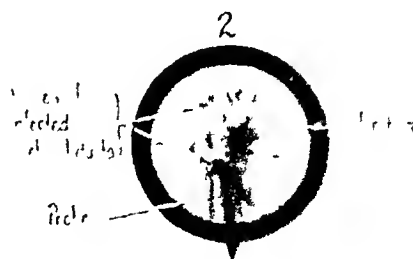
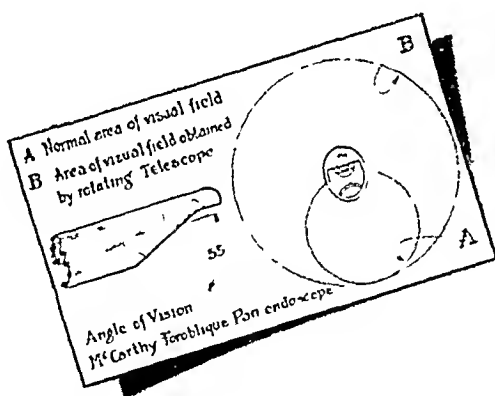
Paris France 584

(Contents continued on page 4)

McCarthy Foroblique Pan-endoscope

This appropriately named cystoscope possesses such broad utility that it has become one of the most widely used instruments in urology.

Essentially the armamentarium consists of straight sheaths, a foroblique telescope and a bridge assembly for relating these elements. Sheaths are available in sizes 16 to 30 Fr. The telescope is the well-known McCarthy Foroblique system noted for its natural, "amphitheatre" visual characteristics.



|| The wide range of usefulness of the McCarthy Pan endoscope is demonstrated by its ability to maintain good vision even to the female urinary meatus ||

The illustration is a reproduction of a series of photographs taken by Mr. J. J. Diduch showing the technique of the Pan-endoscope. The endoscope is inserted into the urethra and a complete examination of the urethra and bladder can be made without the need for a separate instrument.

ESTABLISHED IN 1900



BY REINHOLD H. WAPPLER

AMERICAN **FREDERICK C. WAPPLER** **MAKERS, INC.**
450 WHITLOCK AVE. **CYSTOSCOPE** NEW YORK, L. S. A.

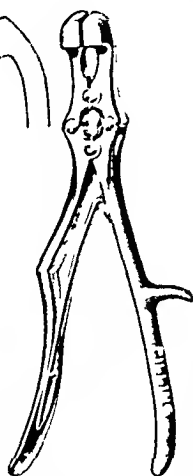
CONTENTS—Continued

THE EFFECT OF RADIATION THERAPY UPON IN- TRACRANIAL GLIOMATA	Loyal Davis, M D Arthur Weil, M D	Chicago Ill 599
THE PLACE OF RADIUM IN THE TREATMENT OF CANCER OF THE BREAST	Geoffrey Keynes, M D	London England 619
INTERSTITIAL RADIATION OF CANCER OF THE BREAST	Leland S McKittrick, M D	Boston Mass 631
THE TREATMENT OF ABDOMINAL CANCERS	Leo Eloesser, M D	San Francisco Calif 645
CARCINOMA OF THE CERVIX TREATED BY THE ROENTGEN RAY AND RADIUM	Joe Vincent Meigs, M D Richard Dresser, M D	Boston Mass 653
CANCER SURGERY	Carl Eggers, M D	New York 666
CARCINOMA OF THE BREAST	Stuart W Harrington, M D	Rochester Minn 690
RESECTION WITH ASEPTIC END-TO-END ANASTO- MOSIS FOR CARCINOMA OF THE COLON	William F MacFee, M D	New York 701
THE DEVELOPMENT OF LABORATORY SERVICE IN A CANCER HOSPITAL	James Ewing, M D	New York 715
ABNORMAL FUNCTION OF THE COMMON BILE DUCT RESULTING FROM BENIGN CONDITIONS	Waltman Walters, M D	Rochester Minn 726
CONGENITAL ATRESIA OF THE BILE DUCTS	Edward J Donovan, M D	New York 737
OBSTRUCTIVE JAUNDICE	Howard C Naffziger, M D Jesse L Carr, M D Frederick S Foote, M D	San Francisco Calif 745
MORTALITY IN ACUTE ILEUS	Frederick T vanBeuren, Jr, M D Beverly C Smith, M D	New York 752

(Contents continued on page 6)

THORACIC

ALL THE INSTRUMENTS
REQUIRED IN
THORACOPLASTY
THORASCOPY
PNEUMOLYSIS
PHRENICECTOMY
LOBECTOMY
PNEUMOTHORAX
DECOMPRESSION
SEND FOR LITERATURE



BABCOCK RUSTLESS STEEL SUTURE

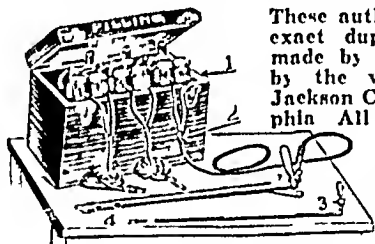
Babcock Rustless steel suture is a doubly annealed steel wire made in six sizes (18, 22, 28, 30, 32 and 35) Circular on request

Four-ounce spool,
any size \$3 00



BRONCHOSCOPY

Pilling-Made Equipment Used by the
Staff of the Chevalier Jackson Clinics



These authentic models are exact duplicates of those made by us for and used by the various Chevalier Jackson Clinics in Philadelphia. All made under our one roof and supervision, insuring proper inter-functioning of separate instruments.

Bronchoscopic Catalog on Request

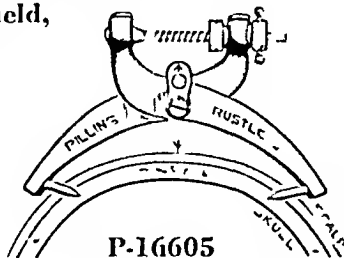
Order direct from us to avoid incorrect models

SKULL TRACTION TONGS

for Fracture Dislocations of the
Cervical Spine

W. Gayle Crutchfield,
M.D., Richmond

Tongs to be applied transversely to the vertex of the skull for purpose of exerting traction on the cervical spine



P-16605

Tongs, drill and drill points \$30 00
reprint on request

George P. **PILLING** & Son Co.
Arch and 23rd Philadelphia

Send for your
FREE COPY of this new
METABOLISM BOOKLET



If you are interested in modern methods of metabolism testing and wish to broaden your service by having up to date metabolism equipment for your own use, send for this brand new free booklet which gives a complete story of the popular Sanborn Metabolism Tester MODEL E-I-S.

Importance of Metabolism Tests

A series of tests will guide the surgeon in treatment of thyroid cases, will indicate when to prescribe medication, when to operate and when to postpone operation. Leading medical authorities agree that routine metabolism tests are justified by their valuable aid to diagnosis and therapy in thyroid disturbances, diseases of the blood, cardiac disorders and some nervous ailments.

How Sanborn MODEL E-I-S meets the need for an accurate, simplified, guaranteed metabolism tester at a low factory price is told in the new 16 page illustrated booklet.

*Mail the coupon below for your
complimentary copy*

Sanborn MODEL E-I-S will be on exhibit at the
Clinical Congress of the American College of
Surgeons, Oct. 25-29 in Chicago

SANBORN COMPANY

A.S. 10

39 O-horn St., Cambridge, Mass.

Please send me a complimentary copy of the
new illustrated booklet about MODEL E-I-S
latest Sanborn Metabolism Tester. No obligation

Dr.

Sir

City

State

CONTENTS—Continued

PERINEPHRIC ABSCESS	Richard H. Miller, M.D.	Boston, Mass. 756
POSTOPERATIVE USE OF INSULIN IN THE NONDIABETIC	Fraser B. Gurd, M.D.	Montreal, Canada 761
SKELETAL TRACTION IN THE TREATMENT OF FRACTURES AND DISLOCATIONS OF THE CERVICAL SPINE	William E. Gallie, M.D.	Toronto, Canada 770
RUPTURE OF THE LUMBAR INTERVERTEBRAL DISK	William Jason Mixter, M.D.	Boston, Mass. 777
ANESTHESIA AND SURGERY	Ralph M. Waters, M.D. Erwin R. Schmidt, M.D.	Madison, Wis. 788

MEMOIR

LIEUTENANT-GENERAL SIR ALFRED KEOGH, G.C.B., G.C.V.O., C.H.	Major-General Sir Michael Russell, K.C.M.B., C.B.
---	---

795

do you treat **CANCER?**

THE RADIUM EMANATION CORPORATION

MAINTAINS the most efficiently organized Radium laboratory to make available to you, at low cost, every facility for the use of Radium in your practice

RADON SEEDS Removable or permanent. We provide seeds of the composite type, with Radon under leak-proof glass seal. Filtration 0.3 mm. of Platinum.

APPLICATORS Uterine tubes, cervical applicators, surface plaques properly prepared to meet the requirements of each individual case.

OUR SERVICE is available to you day and night including Sundays and holidays. Your inquiries and orders will receive our prompt and careful attention.

THE RADIUM EMANATION CORPORATION

GRAYBAR BLDG

Tel. MOhawk 4-6455

NEW YORK, N. Y.

VINETHENE

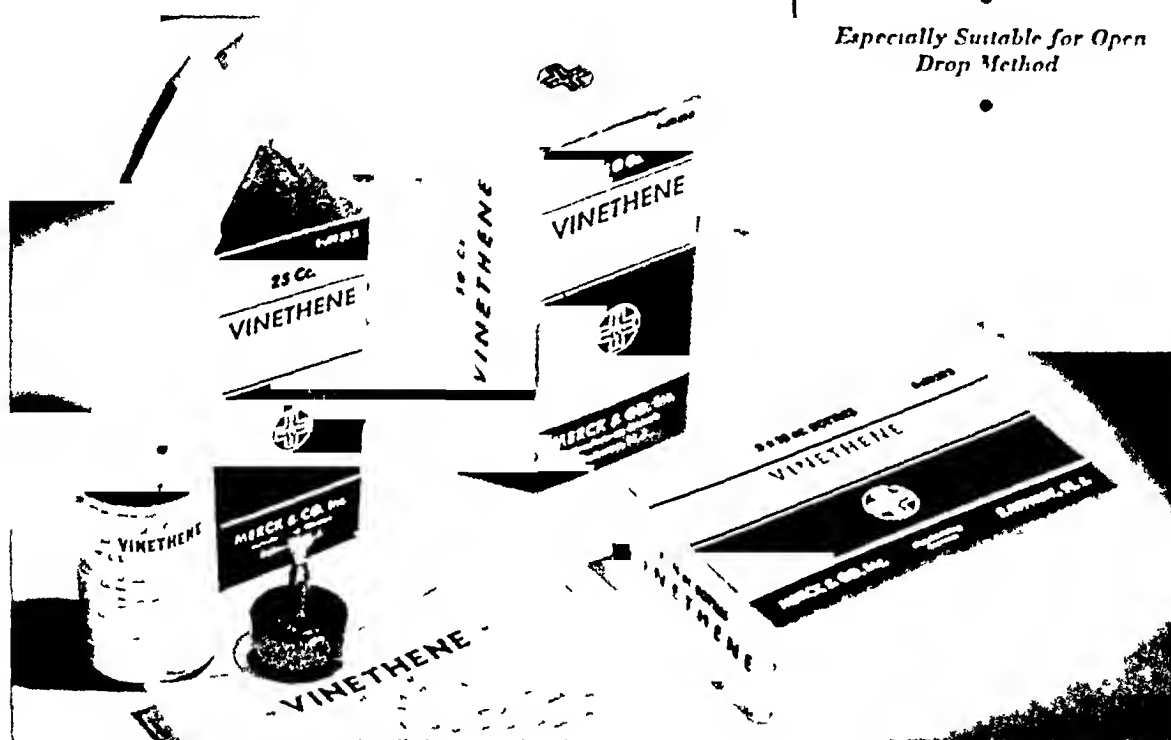
PEG U S PAT OFF

Vinyl Ether for Anesthesia

MERCK

A NEW INHALATION ANESTHETIC

Council  *Accepted*



An Inhalation Anesthetic
for Short
Operative Procedures

- *Rapid Induction*
- *Adequate Relaxation*
- *Rapid Recovery*
- *Infrequent post anesthetic
Nausea or Vomiting*

*Especially Suitable for Open
Drop Method*

Vinethene is useful in short procedures such as reduction of fractures, incision and drainage of abscesses, dilatation and curettage, myringotomy, repair of lacerations, and painful dressings. For general minor surgical use Vinethene is also supplied in small containers convenient for the physician's bag. Boxes of 3—10 cc vials with a special dropping cap.

MERCK & CO. INC., Rahway, New Jersey

Please send detailed information regarding Vinethene

Name M D

Street

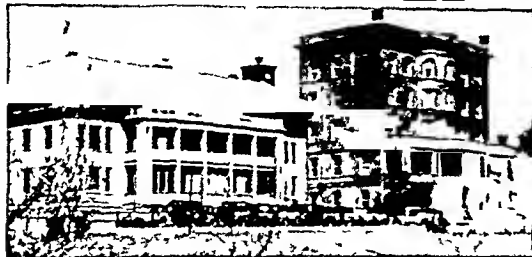
City State

MERCK & CO. Inc.

Manufacturing Chemists

RAHWAY, N. J.

USERS OF BERBECKER NEEDLES



GARFIELD MEMORIAL HOSPITAL Washington, D C

Founded 1882, to perpetuate the memory of President James A. Garfield by carrying out his earnest wish for a general hospital in Washington, D C. Represents, also, the ideals and tangible assistance of many distinguished men of the President's time. Today—well staffed, and equipped in the modern manner—it offers efficient service to all regardless of race, creed or ability to pay.

JULIUS BERBECKER & SONS, INC
15 E 26th St., New York, N Y

**BERBECKER
SURGEONS
NEEDLES**

IN THE
BLUE
PACKET

Cook County Graduate School of Medicine

(In affiliation with Cook County Hospital)
Incorporated not for profit

ANNOUNCES CONTINUOUS COURSES STARTING EVERY WEEK

MEDICINE—Informal Course first of every week, Intensive Personal Courses Special Courses

SURGERY—General Courses One Two Three and Six Months Two Weeks' Intensive Course in Surgical Technique with practice upon living tissue, Clinical Course Special Courses

GYNECOLOGY—Diagnostic Courses Clinical Courses Special Courses starting every week

FRACTURES & TRAUMATIC SURGERY—Informal Practical Course Ten Day Intensive Course starting October 11th

OTOLARYNGOLOGY—Two Weeks' Intensive Course starting April 4, 1938

OPHTHALMOLOGY—Two Weeks Intensive Course starting April 18 1938 Personal Course in Refraction

UROLOGY—General Course Two Months Intensive Course Two Weeks Special Courses
CYSTOSCOPY—Ten Day Course every two weeks

General, Intensive and Special Courses in all branches of Medicine and Surgery starting every week

TEACHING FACULTY

Attending Staff of Cook County Hospital

Address Registrar, 427 South Honore Street
Chicago Illinois

INDEX TO ADVERTISERS

SURGICAL SUPPLIES

	Page
American Cystoscope Makers, Inc	3
Berbecker	8
Clay-Adams Company	22
Kny-Scheerer Corporation	Inside Back Cover
Modern Surgical Instrument Co	24
George P. Pilling & Son Co	5
Sanborn Company	5
J. Sklar Mfg. Company	1
Taylor Instrument Companies	28

LIGATURES

Davis & Geck, Inc	16
Davis & Geck, Inc	Insert 8-9
Gudebrod Bros. Silk Co	22
Johnson & Johnson	15
O. De Witt Lukens Co	16

X-RAY PLATES

Eastman Kodak Company	19
General Electric X-ray Corporation	23
Radium Emanation Corporation	6

PHARMACEUTICAL SUPPLIES

Anglo-French Drug Co., Inc	Inside Front Cover
Armour Laboratories	10
Ciba Pharmaceutical Products, Inc	Back Cover
Hoffmann-La Roche	11
Eli Lilly & Company	13
Loeser Laboratory	Back Cover
Merck & Co., Inc	7
National Drug Company	17
Parke, Davis & Company	9
Petrolagar Laboratories, Inc	25
Purdue Frederick Company	Inside Back Cover
Schering & Glatz, Inc	21
E. R. Squibb & Sons	14
William R. Warner & Co	27
Winthrop Chemical Co., Inc	12
Ulmer Pharmacal Co	24

HOTEL

Chalfonte-Haddon Hall	26
-----------------------	----

PUBLISHERS

Lea & Febiger	20
J. B. Lippincott Company	18, 24, 26

SCHOOLS

Cook County Graduate School of Medicine	8
Harvard Medical School	26



SPECIALIZATION

A seventeenth century lens-maker improves the microscope — micro-organisms become visible — and a chain of discovery follows which revolutionizes surgery. Thus, civilization marches ahead in the footsteps of specialists.

- In the production of surgical sutures, specialization has many advantages. Here improvements come, not by accident, but through long and extensive research.

- Special equipment and the undivided effort of an experienced personnel are vital to the maintenance of present standards.

- Advancement demands a staff fully qualified to apply to our special field all important developments in allied sciences.

Yesterday, today, tomorrow — *"The One Thing We Do"* Adherence to this slogan is reflected in the leadership of our products.

DAVIS & GECK SUTURES

DAVIS & GECK, INC., BROOKLYN, NEW YORK, U. S. A.

Special D&G Sutures

WITH SWAGED-ON ATRAUMATIC NEEDLES

THIS group of products comprises over a hundred suture and needle combinations specially designed for specific procedures, particularly those in which minimized suture trauma and the convenience of needles which cannot possibly become unthreaded, are desirable. A few products from this group are shown on these pages. Full information on others may be obtained from your dealer or by mail from us, upon request.

Intestinal Sutures

KALMERID plain or chromic catgut, celluloid-linen or silk with Atraumatic needles in the several types indicated integrally affixed. Suture lengths 36 inches for products 1342, 1352, 1372 and 1542, all others 28 inches.

1 HIRMO-1111 (non-boilable)

Plain Catgut

NO		NEEDLE	DOZEN
1501	Straight Needle	A-1	\$3 60
1503	3/8-Circle Needle	A-3	4 20
1504	Small 1/2-Circle Needle	A-4	4 20
1505	1/2-Circle Needle	A-5	4 20

20-Day Chromic Catgut

1541	Straight Needle	A-1	\$3 60
1542	Two Straight Needles	A-1	4 20
1543	3/8-Circle Needle	A-3	4 20
1544	Small 1/2-Circle Needle	A-4	4 20
1545	1/2-Circle Needle	A-5	4 20

1 CAUSIRO-1 HERMAI (boilable)

Plain Catgut

1301	Straight Needle	A-1	\$3 60
1303	3/8-Circle Needle	A-3	4 20
1304	Small 1/2-Circle Needle	A-4	4 20
1305	1/2-Circle Needle	A-5	4 20

20-Day Chromic Catgut

1341	Straight Needle	A-1	\$3 60
1342	Two Straight Needles	A-1	4 20
1343	3/8-Circle Needle	A-3	4 20
1344	Small 1/2-Circle Needle	A-4	4 20
1345	1/2-Circle Needle	A-5	4 20

Intestinal Sutures (cont'd)

Celluloid-Linen

NO		NEEDLE	DOZEN
1351	Straight Needle*	A-1	\$3 60
1352	Two Straight Needles*	A-1	4 20
1354	Small 1/2-Circle Needle*	A-4	4 20

Black Silk

1371	Straight Needle*	A-1	\$3 60
1372	Two Straight Needles*	A-1	4 20
1374	Small 1/2-Circle Needle*	A-4	4 20

Sizes 00 0 1, except *00 0 only

In packages of 12 tubes of a kind and size

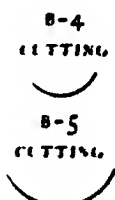


A 1

DIAMETER .22 TO .26

Eye Sutures

FINE sizes of plain, 10-day chromic catgut, and black silk with small Atraumatic needles. Suture length 18 inches except as noted. Boilable.



NO.	MATERIAL	SIZE	LENGTH
1661	Black Silk	6-0	11-3
1663	Plain Catgut	4-0	11-5
1665	Black Silk	6-0	11-1
1665	Black Silk	4-0	11-1
1667	Plain Catgut	3-0	11-4
1669	10-Day Catgut	4-0	11-5
1669	10-Day Catgut	3-0	11-5
1669D	10-Day Catgut †	4-0	11-5
1669D	10-Day Catgut †	3-0	11-5

DOUBLE ARMED

1662	Black Silk *	6-0	11-3
1664	Black Silk *	6-0	11-1
1664	Black Silk *	4-0	11-1
1666	Plain Catgut *	3-0	11-4
1668	10 Day Catgut *	4-0	11-5
1668	10-Day Catgut *	3-0	11-5
1668D	10-Day Catgut †	4-0	11-5
1668D	10-Day Catgut †	3-0	11-5

* 12 inches † 9 inches

Package of 12 tubes of a kind \$4.20

Cleft Palate and Harelip Sutures



NO.	MATERIAL	SIZE	LENGTH
1751	Kal-dermic	00	C-1
1752	Aluminum-Bronze Wire	00	C-1
1753	Black Braided Silk	000	C-2
1754	Aluminum-Bronze Wire	00	C-3
1755	Kal-dermic	00	C-3
1758	Aluminum-Bronze Wire	00	C-3

Suture length 18 inches

Package of 12 tubes of a kind \$4.20

Thyroid Sutures

THERMOFILIN (permanently absorbable) ThermoFilin Catgut and black braided silk with half-circle, taper point Atraumatic needles. Suture length 28 inches.

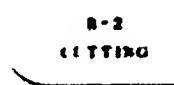


NO.	MATERIAL	SIZE	LENGTH
1635	Non-Boilable Plain Catgut	C	11-1
1625	Boilable Plain Catgut	C	11-1
1624	Black Braided Silk	C	11-1

Package of 12 tubes of a kind \$4.20

Plastic Sutures

FINE sizes of Kal-dermic, silk and silk-worm gut with small, cutting point Atraumatic needles. Suture length 18 inches. Boilable.



NO.	MATERIAL	SIZE	LENGTH
1651	Kal-dermic	8-0	11-1
1651	Kal-dermic	6-0	11-1
1652	Kal-dermic	8-0	11-5
1652	Kal-dermic	6-0	11-5
1652	Kal-dermic	4-0	11-5
1653	Black Silk-worm	4-0	11-1
1655	Kal-dermic	4-0	11-2
1658	Black Silk	4-0	11-2

Package of 12 tubes of a kind \$4.20

Other D & G Sutures

SPECIAL needled sutures are also prepared for dental, tonsil, circumcision, obstetrical, ureteral, renal, nerve, artery, and emergency work. These are in addition to our complete line of unneedled sutures embracing catgut, ribbon gut, kangaroo tendons, and a variety of other non-absorbable materials.

DISCOUNTS ON QUANTITIES

DAVIS & GECK, INC., 217 DUFFIELD STREET, BROOKLYN, NEW YORK

Copyright 1937 Davis & Geck, Inc. Printed in U.S.A.



BARTHOLOMEO DE AGUERO of Seville (c1600) fought bitterly against the practice of stuffing wounds with foreign matter to promote suppuration. Also he decried abuse of the suture by those who charged their patients by the stitch. He recommended clean hygienic surgery with simple dry suture, and such was his success that the saying "I place my life in the hands of God and de Aguero" became general among the people of Spain.

D & G Sutures

"THEY ARE HEAT STERILIZED"

DAVIS & GECK INC



*Easily and Conveniently
Administered*

MAPHARSEN

MAPHARSEN is easily and quickly prepared for injection. Single doses can be dissolved in syringe and ampoule, without necessitating the use of sterile beakers or other apparatus.

In contrast to the arsphenamines, Mapharsen solutions do not become more toxic on standing; agitation or exposure to air does not increase their toxicity. Haste in completing injections immediately after preparation of solutions is unnecessary.

With the patient either in a sitting or recumbent position, injection can be made according to the usual intravenous technique. Mapharsen solutions should be injected *rapidly*—at the rate of 10 cc. (the entire dose) within 30 seconds after the needle is in place.

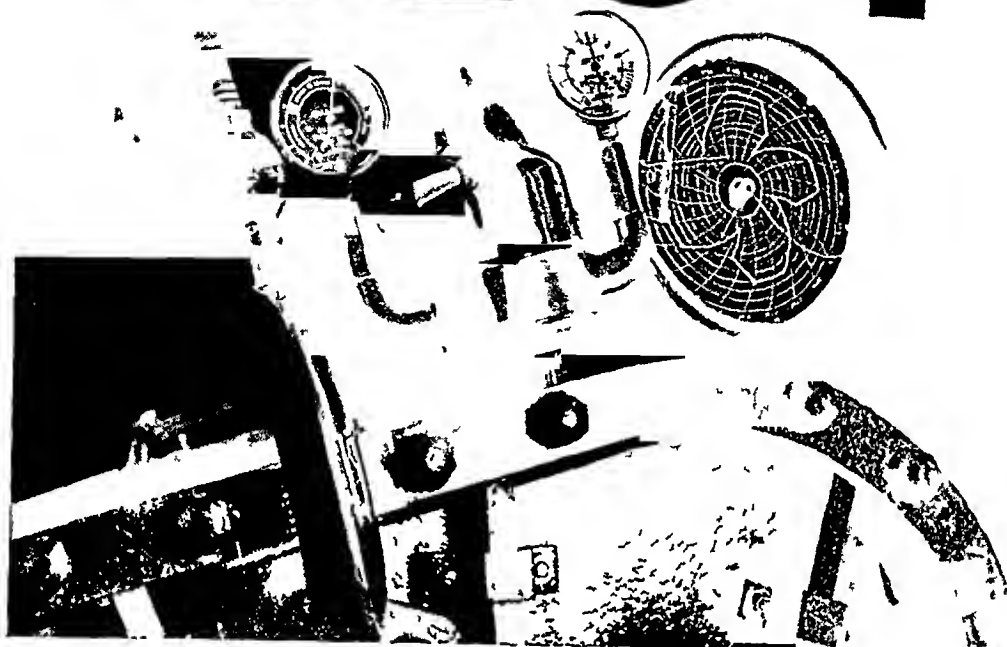
Mapharsen treatment is conveniently administered. The ease and rapidity of injection minimize discomfort and encourage patient cooperation.

Mapharsen (meta-amino-para-hydroxy-phenylarsine oxide hydrochloride) is available in single dose ampoules containing 0.04 and 0.06 Gm. each in individual packages with or without distilled water. It is also supplied in ten dose ampoules, containing 0.4 and 0.6 Gm. for use by hospitals and clinics.

PARKE, DAVIS & COMPANY

THE WORLD'S LARGEST MAKERS OF PHARMACEUTICAL AND BIOLOGICAL PRODUCTS

320° F



All Armour Sutures and Ligatures are Heat Sterilized at 320° F. for 90 Minutes

VISIT THE ARMOUR BOOTH AT THE CLINICAL CONGRESS

Surgeons attending the Clinical Congress of the American College of Surgeons, are cordially invited to visit the Armour Laboratories while in Chicago. We welcome the opportunity to show you our equipment and processes in the making of Armour Sutures and Ligatures, and Glanoid Endocrine Products. Attendants at the Armour Booth, No. 102, Stevens Hotel, will gladly arrange a tour of inspection for you.

STERILITY is the prime requisite of a ligature or suture. Heat sterilization is the recognized method of assuring suture safety. Armour Sutures and Ligatures are heat sterilized. They are held at a temperature of 320° F. for 90 minutes.

This process is costly. It takes extra time. But it insures complete freedom from all pathogenic organisms. It provides the extra margin of safety to which surgeons are entitled, regardless of time or expense.

Upon completion, all Armour Sutures and Ligatures are quarantined for a 16 day period, prior to distribution. During this quarantine, modern scientific tests are made to establish their sterility. If for any reason the sutures do not pass these tests, they are destroyed. Armour Sutures and Ligatures have other vital qualities. They have a high degree of tensile strength and pliability. They are microscopically uniform in gauge. These qualities, like sterility, are proved by painstaking tests and scientific techniques. You can rely on Armour Sutures for the most exacting surgery. Yet they cost no more to use.



Armour Sutures on Non-Traumatic Eyeless Needles

20-day Chromic

on One Straight Intestinal Needle

No. 00, 0

on Two Straight Intestinal Needles

No. 00, 0

on Curved Intestinal Needle

No. 00, 0

on Half Circle Intestinal Needle

No. 00, 0

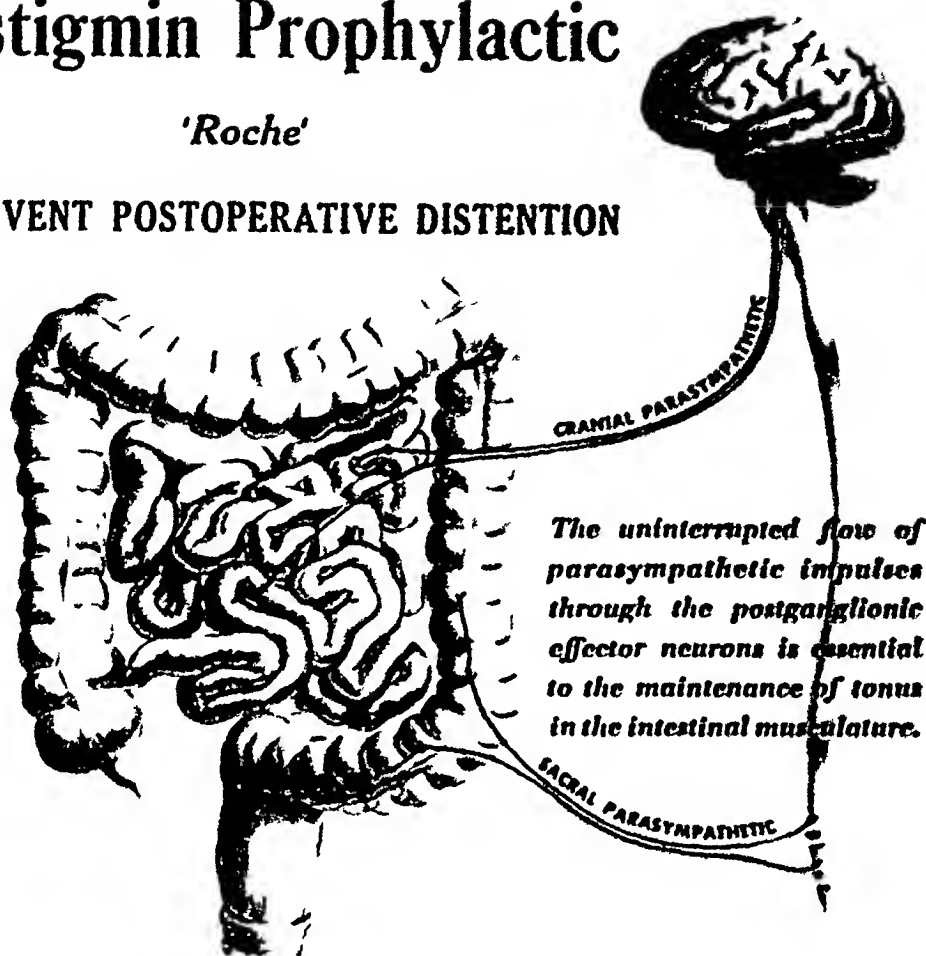
THE ARMOUR LABORATORIES

ARMOUR AND COMPANY Union Stock Yards, Chicago

Prostigmin Prophylactic

'Roche'

TO PREVENT POSTOPERATIVE DISTENTION



"REVIEW of the 88 cases forming the basis of this report shows that prostigmin prophylactic has been most valuable in combating the much dreaded symptoms of postoperative distention and gas pains. In comparing these case records with an analogous series prior to our use of prostigmin prophylactic we have found that distention and gas pains have been reduced to a negligible minimum" Lewis and Axelman, "Modern Method for Prevention of Postoperative Distention," *The American Journal of Surgery*, May, 1936, pp 308-312

"In our experience prostigmin, used by intramuscular injection, has proved to be a very reliable agent

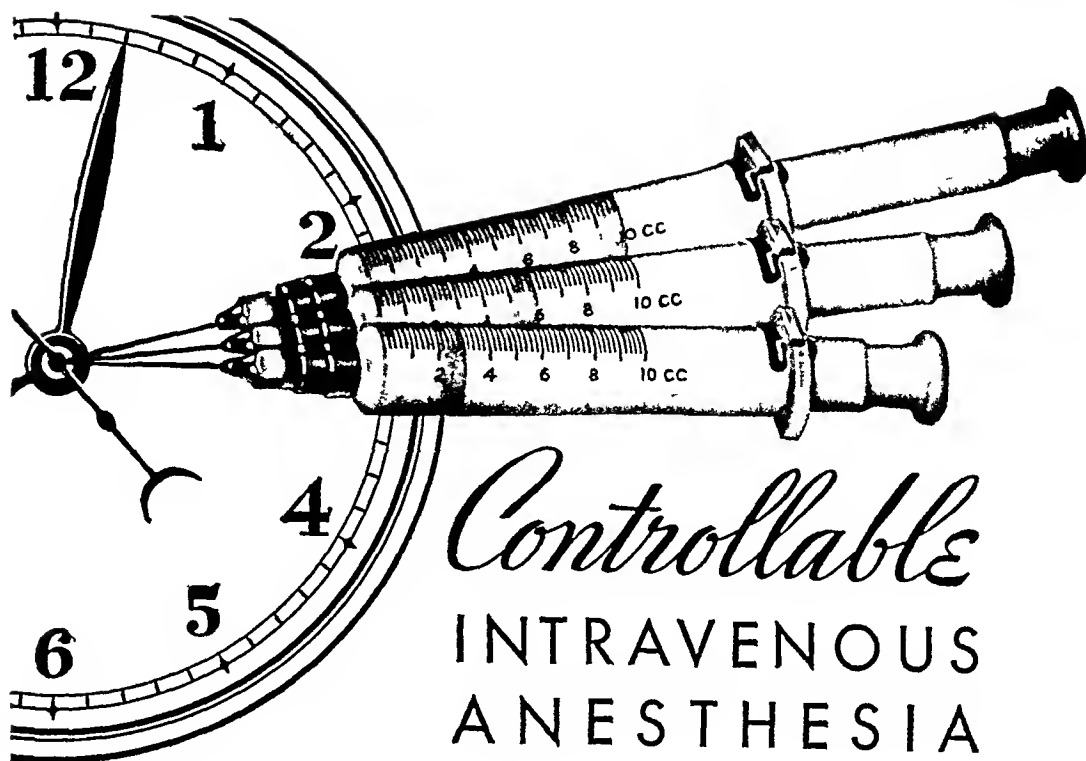
to restore early normal peristalsis following laparotomy. Gas pains are greatly diminished if not completely avoided. Nausea, if present, is indirectly reduced in duration." Schlaepfer, "Relief of Postoperative Intestinal Atony with Prostigmin," *The Western Journal of Surgery, Obstetrics, and Gynecology*, July, 1936

"Our results indicate that prostigmin is of value both as a prophylactic agent and a treatment for paralytic ileus and distention." Uznanski, "A New Treatment for Paralytic Ileus," *Illinois Medical Journal*, December, 1936, 70:567-569

PACKAGES

For prevention: Prostigmin Prophylactic Roche—blue cartons—ampuls 1 cc (1:4000 solution)—cartons of 12 and 100
For treatment: Prostigmin Roche—buff cartons—ampuls 1 cc (1:2000 solution)—cartons of 12 and 100

HOFFMANN-LA ROCHE • INC • NUTLEY • N. J.



Controllable INTRAVENOUS ANESTHESIA

THE voluminous and increasing literature demonstrates that Evipal Soluble produces surgical anesthesia quietly and without delay. Disintegration of this synthetic in the body is so rapid that awakening takes place after fifteen or twenty minutes without nausea, vomiting or excitement.

The newer refinement of administration technic—intermittent injection—makes it possible to maintain control of the effect of Evipal Soluble to a degree which has been compared with that of inhalation anesthetics.

EVIPAL SOLUBLE

Evipal Reg U S Pat Off & Canada

Brand of CYCLURAL SODIUM

(Sodium salt of N methylcyclohexenylmethyl barbituric acid)

Evipal Soluble is supplied in ampules containing 0.5 Gm and 1 Gm of the sterile powder

Write for a copy of "Evipal Soluble, Intravenous Anesthetic"



WINTHROP CHEMICAL COMPANY, INC.

Pharmaceuticals of merit for the physician

NEW YORK, N. Y.

WINDSOR, ONT.

Factories Rensselaer, N. Y.—Windsor, Ont.



'Metycaine'

(CINMA-[2-METHYL-PIPERIDINO] PROPYL
BENZOATE HYDROCHLORIDE, 1:115)

Spinal Anesthesia

A special 10 percent 2-cc ampoule is supplied for this purpose. The duration of spinal anesthesia with 'Metycaine' is as much as 50 percent longer than is obtained with a corresponding dose of procaine. The anesthesia appears more promptly and is more intense. These ampoules, properly diluted, may also be used for local infiltration, field block, and nerve block.

Topical Application

In urology, rhinology, gynecology, and ophthalmology 'Metycaine' is frequently useful in concentrations of 1 to 1 percent. It

may be used before cystoscopy or operative work in the bladder. Before instrumentation in the nose or throat 'Metycaine' is frequently applied as a spray. Minor and major surgical procedures on the eyeball may be preceded by instillations of 'Metycaine'.

Infiltrative Anesthesia

'Metycaine' is used by subcutaneous and intramuscular injection to anesthetize operative fields. Solutions of 1.1 to 2 percent are recommended. In proctology 'Metycaine' may be used for the necessary nerve blocking before hemorrhoidectomy and is effective postoperatively to relieve pain and tension.

. . .

Suitable prescription forms are available for all of the above purposes. Literature will be supplied to physicians upon request.

ELI LILLY AND COMPANY

Principal Offices and Laboratories, Indianapolis, Indiana, U. S. A.

Cyclopropane Anesthesia in Thyroid surgery



DISCUSSING anesthesia for thyroid surgery at the Lahey Clinic, Sise¹ has stated "Cyclopropane appears to offer the best anesthesia for thyroid surgery since it combines better than any other the two necessary factors, efficiency and low toxicity. It is also possible to use it with abundant oxygen, and it lends itself better than any other gas to the carbon dioxide absorption method of anesthesia and to the use with it of helium."

The smooth, rapid induction, ease of control, quiet breathing and rapid recovery are other features which commend the use of cyclopropane in thyroid surgery.

Squibb Cyclopropane, like all other products bearing the Squibb label, is subjected

to elaborate chemical, physical and biological tests to insure its purity and efficacy. For this reason it has been accepted by anesthetists throughout the country.

Squibb Cyclopropane is supplied in 30-, 75- and 200-gallon cylinders and in 2-, 6- and 25-gallon Amplons*. The 30 gallon cylinders and the 2- and 6-gallon Amplons are especially suitable for portable machines.

Note Because of the great potency of cyclopropane in low concentrations it is important that the anesthetist be thoroughly familiar with the technique of its administration.

For a booklet on Cyclopropane address the Anesthetic Division, 745 Fifth Avenue, N. Y.

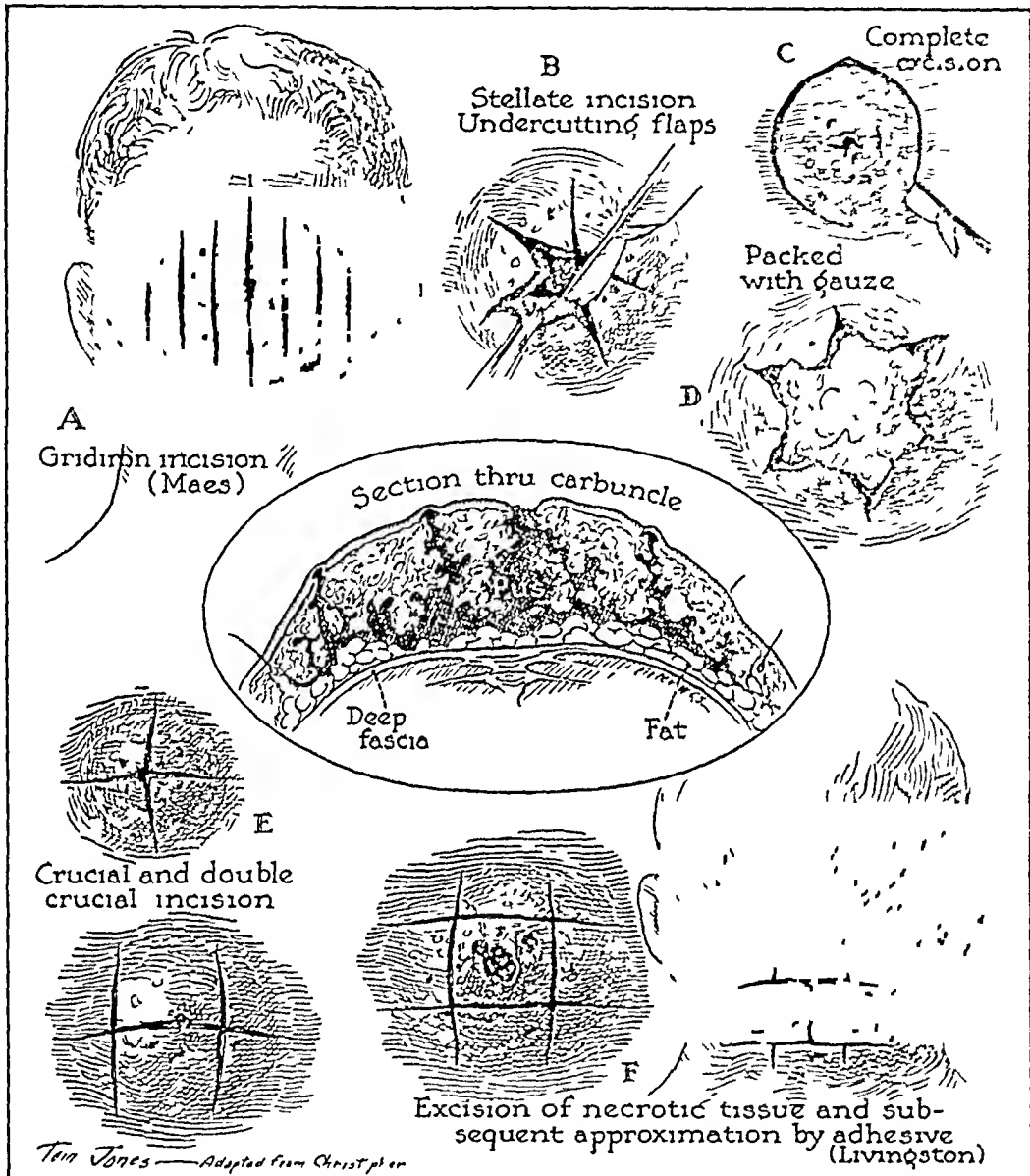
E·R·SQUIBB & SONS, NEW YORK
MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858

¹ Sise, I. F. Anesthesia for Thyroid Surgery. *J. Indiana State M.* 4: 30-100 April 1937.

* Amplon is a trade mark of F. R. Squibb & Sons.

OPERATIVE PROCEDURE LXXIV

Surgical Treatment of Carbuncle



Johnson & Johnson began producing surgical sutures in 1887. Our experience of the last 49 years has led us to the production of what thousands of surgeons in all parts of the world consider the most dependable catgut ever devised—Ethicon Sutures. Our scientific staff includes the most capable men available, who devote their entire time to experiment and control in our laboratories in the United States, Canada, England and Australia.

ETHICON NON-BOILABLE CATGUT SUTURES

JOHNSON & JOHNSON, NEW BRUNSWICK, N. J., CHICAGO, ILL.
MANUFACTURERS OF SURGICAL SUTURES SINCE 1887

Lukens Sterile Catgut

TRADE (Bartlett Process) MARK



Make the Test Yourself
Compare It Point for Point With any Other Catgut
We Will Send the Samples

Sizes 00-4 Plain

C. DE WITT LUKENS CO.
4908 Laclede Ave.
ST. LOUIS, MO., U.S.A.

Sizes 00-4 Tanned

**Sutures for
every surgical
situation**



DAVIS & GECK, INC., 217 DUFFIELD STREET, BROOKLYN, NEW YORK

ANNALS OF SURGERY

VOL 106

OCTOBER 1937

No 4



TRANSACTIONS OF THE AMERICAN SURGICAL ASSOCIATION

MEETING HELD IN NEW YORK, N Y

ADDRESS OF THE PRESIDENT

SAMUEL GROSS LOOKS IN ON THE AMERICAN SURGICAL
ASSOCIATION

EVARTS A GRAHAM, M D
St Louis, Mo

FROM THE DEPARTMENT OF SURGERY, WASHINGTON UNIVERSITY AND BARNES HOSPITAL

IN ORGANIZATIONS similar to the American Surgical Association it has become traditional for the president to make an address at the beginning of the meeting. For the most part the presidential addresses before this organization have been in the nature of scientific papers. Some of them, however, have been striking oratorical composition on historic, moral or educational aspects of our profession. A few others have had a practical bearing upon the affairs of our Association, offering suggestions concerning changes in its scope, composition, or administration. The latter type of address, in my opinion, has been far too infrequent for the welfare of the organization. It has seemed to me that it might be well this year, 58 years after the birth of this Association, to give consideration to the purposes which the founders had in mind, to ask ourselves whether or not these purposes have been carried out and to make an effort to determine if the course which the Association has followed seems to be a satisfactory one to hold to in the future. It is an interesting fact that despite the permanence of organizations like this the president has only one opportunity to address the members in his official capacity. His remarks therefore are as much in the nature of a valedictory as of an inaugural address. He serves really only momentarily as the chief administrative officer. Perhaps that is the reason why some of the topics which I wish to present to you have not attracted the attention of, or at least have been ignored by, other presidents.

If we enquire into what objects the founders of this Association had when it was created, we can find the answer, I think, in the address of welcome by Gross, the president, at the meeting in Philadelphia, May 31, 1882, who said

"The question has been asked, perhaps pertinently enough, what need is there of such an organization as this, seeing that the country is full of all sorts of medical societies? The answer is not difficult, at all events, I do not find it so. We have in the United States, according to a reasonable estimate, not fewer than 60,000 medical men. Among these are large numbers of surgeons, who, in point of culture, practical skill, and reputation as writers and teachers, would be an honor to any country, however high its standard of excellence. To unite these men into one harmonious whole, for the benefit of all, is one of the main objects which the founders of the American Surgical Association had in view when they met in Atlanta, in May, 1879. If it be said that we are striking a blow at the American Medical Association, we deny the soft impeachment. On the contrary, we shall strengthen that body by rousing it from its Rip Van Winkle slumbers, and infusing new life into it. We can hurt no society now in existence, or likely to come into existence. We can hurt only ourselves, if we fail to do our duty. We hope to make the American Surgical Association an altar upon which we may annually lay our contributions to Surgical Science, and so show to the world that we are earnest and zealous laborers in the interest of human progress and human suffering. The whole field of surgery, from the structure of a boil upon a man's face to an amputation of the hip-joint, is undergoing revision. New avenues are constantly being opened, and the importance of the study of physiology, in its relations to practical surgery, is daily becoming more and more apparent. In short, in whatever direction we cast our eyes, nothing but the most substantial encouragement greets our vision, and urges us on to increased exertion."

It seemed to me that it would be of great interest to all of us to have our founder, Gross, come back and give us an appraisal of the activities and accomplishments of the American Surgical Association. Accordingly, I took advantage of my prerogatives as president and invited him to be here this morning. Although he may be invisible to you I am sure you will be able to hear his spirit speak.

DOCTOR GROSS. When I received your radio message, Mr. President, inviting me to attend this meeting of the American Surgical Association, at first I had some hesitation about accepting. I feared that the trip might be too exhausting. The transportation facilities from heaven to earth, however, have been so greatly improved that I found that by coming down a radio beam the trip was really delightful. But I was told by some of my friends that no improvement in the transportation from earth to heaven has occurred and that it would, therefore, be very difficult to make the return trip. Nevertheless I was willing to take a chance on that, despite the fact that Saint Peter cautioned me that it is especially difficult to get to heaven from New York.

THE PRESIDENT We feel greatly pleased, Doctor Gross that you have honored us by coming to this meeting I should like to take advantage of your visit to discuss with you some of the affairs of this Association which you created

DOCTOR GROSS Gentlemen it is a great pleasure to me to see that the American Surgical Association is still an active organization In the 58 years that have elapsed since its first meeting many changes must have occurred both in surgery itself and in this Association

THE PRESIDENT Yes, Doctor Gross, you will scarcely believe me when I tell you of some of the achievements of surgery In the larger clinics of the present time operations on nearly all of the organs and systems of the body are performed almost daily with mortalities which would seem incredibly low to you if I should tell you of them

DOCTOR GROSS You must be exaggerating, Mr President, when you speak of operations on nearly all of the organs of the body as of almost daily occurrence Doubtless you are referring only to the abdominal and pelvic organs Surely you do not mean to include such organs as the brain, the thyroid, the lungs, and certainly not the heart

THE PRESIDENT No, I am not exaggerating Even the organs which you mention are frequently the point of attack of operations today, and I might mention others which may seem even more strange to you, namely the adrenals and the pituitary gland

DOCTOR GROSS But for what conditions are operations performed on so many of the various organs? I can't imagine how surgical lesions could be numerous enough to justify the frequent operations

THE PRESIDENT The answer is to be found in the fact that surgery has encroached on the field of medicine to such an extent that many conditions which in your day were regarded as purely medical are now recognized as having surgical aspects For example, pulmonary tuberculosis certain forms of heart disease and even high blood pressure have become to a considerable extent surgical problems I could mention many others Tumors are being removed successfully from the brain, the heart is being directly attacked by operation and even whole lungs are being removed successfully for cancer and other conditions

DOCTOR GROSS I am amazed at what you say How can you tell when an operation is indicated on many of the organs which we have mentioned? How can you diagnose what you call surgical lesions of those organs which you cannot palpate or see?

THE PRESIDENT The field of diagnosis has likewise expanded enormously By means of a revolutionary discovery of Roentgen since your day we can now see indirectly many of the organs which were invisible to you and your

colleagues, and by means of various other appliances we can actually see into the different orifices of the body and learn of the condition of many of the organs in that way. Chemical tests of different kinds assist us in determining derangements of function of many of the viscera and help us in that way to localize the chief center of the disease.

DOCTOR GROSS: It must be difficult for the student to learn all of these things. How is he taught them? I should think it would be still more difficult for any one individual to be adept at all these procedures and at the same time to be able to operate skillfully on all of the organs of the body.

THE PRESIDENT: Your inferences are quite right. In order to learn to use even some of the procedures which I have in mind and to acquire an expert knowledge of the significance of the findings obtained by them much practice with them is required. Similarly in order to acquire an expert skill in handling the disorders of the various organs it is recognized that years of training are necessary. For that reason not only has the period of undergraduate instruction been greatly lengthened since your day but other developments also have occurred. Young men now are compelled to spend several years of intensive training in surgery after their graduation from a medical school if they wish to gain recognition as surgeons. Moreover, specialization has occurred in many regions of the body and there is a strong tendency nowadays for the specialists in one part of the body to post "No Trespassing" signs as a warning for others to keep off. For example, a large active group has arisen who are often known as "Genito-Urinary" surgeons.

DOCTOR GROSS: I suppose the latter group include the gynecologists who were beginning to assert themselves in my day.

THE PRESIDENT: Oh, no! It is not surprising that you don't understand. Specialization is much sharper today. The genito-urinary surgeons seem to be interested in the genital organs of not only the male sex but in the urinary organs of both sexes.

DOCTOR GROSS: I can scarcely believe that.

THE PRESIDENT: The situation must seem strange to you because I understand that all of you who organized the American Surgical Association were general practitioners who did not even confine your work to surgery. There are now, besides genito-urinary surgeons and gynecologists, orthopedic surgeons, neurologic surgeons, thoracic surgeons, plastic surgeons, industrial and traumatic surgeons, proctologists and other varieties almost too numerous to mention.

DOCTOR GROSS: The development of specialization was apparent in my day, but it is amazing that it could have gone to such extremes as your remarks indicate. I suppose, however, that because of the rapid development of surgical knowledge and because of the natural limitations of the human

mind, much specialization has become necessary and even desirable. I fancy, however, that the specialists might have run wild and pursued their specialties to the neglect of the fundamentals of surgery if it had not been for the influence of the American Surgical Association. I am glad now that in my address, in 1882, I stated, in speaking of the surgeons of the country, "To unite these men into one harmonious whole, for the benefit of all, is one of the main objects which the founders of the American Surgical Association had." How fortunate it must have been that there has been such an organization!

THE PRESIDENT I am sorry, Doctor Gross, that I cannot tell you of any great influence of that sort which this Association has exercised. Until the last two or three years the feeling has existed that only those who are so-called general surgeons should be made members, although it is rather difficult to determine what that designation implies. If, however, one who was already a member became a specialist later, that fact was not considered sufficient grounds for his expulsion. In other words, there was no element of disgrace about it. In fact, it was done by some of our best people. Recently, however, the bars have been let down a trifle to admit an occasional avowed specialist. You see we are thoroughly scientific and we wish to experiment to see what harmful influence, if any, a few specialists may have on us. We may not be able to tell for several years because, since we meet only once a year, the exposure to the contamination is not very great. You see our idea has evidently been just the opposite of yours. We have not tried to influence specialization by helping it along a proper course and by assisting those who have tried to prevent it from running wild, but we have kept aloof from the specialists in order to keep ourselves pure.

DOCTOR GROSS I can't understand that attitude. The only explanation which occurs to me is that, because of the enormous increase in the scope and in the amount of surgery which is now being performed, it has become necessary to enlarge the membership of the Association to so great an extent that it would be unwieldy if any considerable number of specialists were admitted.

THE PRESIDENT Your explanation would probably arouse a difference of opinion among the members of the Association. In your day the population of the country was approximately 50 millions. Now it is about 130 millions. On the other hand I notice that, in 1883, the first year in which I could find a list, there were 94 active members and now this number has increased to only 161. In other words, the population of the country has increased 160 per cent but the active membership of this Association only 71 per cent since 1883. Moreover, nowadays the surgeons of the country, even those who limit their practice to surgery, are numbered in the thousands, although in your day there were apparently none who so sharply limited their work. You see, therefore, that the membership of the Association has not

been enlarged to anything like the extent which you might think. Some of the special surgical societies have memberships nearly as large as that of our own, and the individual members of those societies must meet requirements which are as exacting as ours. Do you think, then, that we have failed to carry out your plan of uniting the surgeons into one harmonious whole for the benefit of all?

DOCTOR GROSS I do not wish, Mr. President, to criticize the Association for not carrying out my original intention, but will you please tell me what objections are raised to increasing the membership substantially so that it will be more representative of the large body of surgeons of the country?

THE PRESIDENT It is difficult for me to state the objections, because I have never heard them clearly expressed. Three years ago the matter came up acutely as the result of the emphasis by Doctor Bevan, in his presidential address, on the desirability of enlarging the membership. At that time the limit of active membership was increased from 150 to 175.

DOCTOR GROSS Why was the number set at 175, Mr. President? I suppose some committee had been studying the question and had found as the result of its analysis that 175 was the proper number of members to accomplish the purposes of the Association. But to me it seems a curious number. I should like to know more about how it was arrived at.

THE PRESIDENT I never heard of any committee appointed to study the question and I have never understood why the decision was reached to limit the number to 175, although doubtless there were good reasons. There seems to be no clearly thought out plan, or for that matter any agreement among the members, as to what the purposes and functions of the Association should be. To some the annual meetings provide a pleasant bit of social relaxation. Others take them very seriously and listen to every paper and every discussion that is given. Still others—and I think they constitute the majority of the membership—listen to the papers in which they think they will be most interested, and in the intervals they spend their time profitably in social intercourse with their colleagues.

DOCTOR GROSS The members were like that in my day, Mr. President, and doubtless if you and I should return for a meeting a hundred years from now we should find them very much the same. But as you were speaking, the thought occurred to me that perhaps, if the membership were enlarged to include more of the specialists, the meeting could be arranged in sections so that papers in one specialty could be grouped together to attract the members interested in that field while perhaps a group of papers in another field were being given in another room. Does that idea seem absurd? Of course, I am not in touch with modern conditions. I am of the horse and buggy era.

THE PRESIDENT Many other organizations have carried out the idea which you have just expressed. Evidently they do not think it absurd. I

suppose, however, that because the average attendance at our meetings is only about 135 it seems somewhat ridiculous to consider dividing that number into sections. Perhaps the fear of interrupting the coziness of our little meetings has had something to do with restricting the membership to its present size.

DOCTOR GROSS. I think I am beginning to understand. You have in mind perhaps a sort of round table so that every member can participate freely in the reading and discussion of papers.

THE PRESIDENT. That may be the idea which some of our members have but unfortunately the meetings don't work out that way. Let me explain. Because we have such reverence for your wisdom we have felt that we should adhere to the custom which you and your colleagues started in devoting three days to the meeting. In fact our present By-Laws state that "the meeting shall continue for three days, unless otherwise ordered by a majority vote." Actually, however, we don't carry out that provision. Ever since I have been a member the meetings have continued for only two and one-half days. I hope you won't censure us too strongly for claiming to follow your precedent although actually we fudge a bit and knock off half a day. The result of all this is that we don't begin to have time enough to give to any but a small fraction of the members an opportunity to present papers or even to enter into the discussions. For example, this year more members who applied for the privilege of giving papers had to be declined than the number of those to whom places on the program could be given. Many members don't ask for places because they feel the chance of being on the program is so small. If the members were asked in rotation to appear on the program each one could give a paper only once in six years. A good deal of resentment has been expressed at times because of inability to get a place on the program and even charges of geographic favoritism are made. Some members have become rather disaffected because they feel that they have been discriminated against by being refused places. As for the discussions it is necessary to limit them very sharply in order to get through the program on time. As a result of that policy very few can discuss the papers.

DOCTOR GROSS. It would seem to be a very simple matter either to lengthen the meeting or to have different sections meeting simultaneously. Another day could probably be added very easily and thus provide space on the program for 10 or 12 more papers. Again if there were some modest attempt to form sections, one afternoon could be devoted to a group of papers on the stomach, for example, in one room and to a group of papers on the central nervous system in another room simultaneously. I cannot understand why you have been willing to experience those difficulties for so many years when they could be remedied so easily. When my colleagues and I created this organization, Mr. President, we included in our membership many teachers because we thought that by doing so the Association would be more likely to

keep abreast of all the developments in surgery and perhaps to exercise more leadership over the new movements in surgical practice than would be the case otherwise. Have you departed from this custom? I can think of no other explanation of your extreme conservatism.

THE PRESIDENT No, Doctor Gross, we have not departed from that custom. On the contrary, I believe we have adhered to it even more intensely than the early members did. A large number of our members hold teaching positions in the various medical schools of the country. Moreover, since your day a number of large private clinics have arisen in which young surgeons receive their training. The result of all this is that almost all the members are engaged in teaching. Individually we are—or at least most of us like to think we are—reasonably progressive. But when we get together in this Association we are so conservative that if you could stay throughout the meeting you would probably notice no appreciable change of any sort over the meetings of your time except that perhaps you might be a little confused at the new words and new conceptions of disease expressed in the papers. You will notice that we even continue to hold our meetings at the same time of year as you did.

DOCTOR GROSS I have noticed that fact. I suppose that since the medical schools terminate their sessions about the first of May, the time which we selected is still the most convenient for most of the teachers.

THE PRESIDENT That is a strange circumstance, Doctor Gross. The medical schools no longer end their sessions about the first of May, but nowadays they usually continue until about the middle of June. The first week of June is about the most inconvenient time of year that could be selected for many of us because of examinations, faculty meetings and all sorts of other activities that arise in connection with the closing of the school year. Year after year we allow the inconvenience to continue because we assume that you in your wisdom would not have chosen this particular week if it were not the best.

DOCTOR GROSS Since so many of you are teachers I am sure you are much interested in giving opportunities to the young men of promise who are planning to devote themselves to a career in surgery. Tell me some of the things which the Association is doing in that respect. I imagine you frequently have stimulating programs devoted to a discussion of the teaching of surgery and that the publications of this Association are regarded by the medical schools and the state examining boards as authoritative expressions of the best thought on this important matter. I also imagine that probably you have a standing committee working on the various problems concerned with the teaching of undergraduate surgery and with the later years of special training which you mentioned earlier. It is easy to see how this Association through a distribution of pamphlets on these subjects from time to time must hold the position of leadership in these important aspects of surgery.

which the founders dreamed for it. Is there a forum of any sort under the auspices of you experienced leaders at which the younger men can express themselves on purely clinical subjects, on the results of original investigations of various kinds, particularly on the important applications of physiology to surgery which were apparent to me long ago, or on ideas of education which they may have? Do you have any provision for junior memberships in this Association whereby young men after a period of probation can be promoted to active membership? As I look around the room this morning it seems to me that there is far too large a proportion of gray hair in the audience. Do you not agree with me, Mr. President, that it is the young men who have the most brilliant ideas and the most enthusiasm?

THE PRESIDENT Yes, Doctor Gross, I do agree with you fully. Perhaps we should not be so conservative a body if either we admitted more young men to active membership or at least established a provision for some sort of junior membership. I am sorry to say that we have not actively interested ourselves in many of the matters which you have just mentioned. There is certainly a need for a forum of the kind of which you have in mind. There are many surgical organizations in the country but none of the sort which you mention. Of the national organizations, not devoted to surgical specialties, the surgical section of the American Medical Association gives an opportunity for only a limited number of papers (and those for the most part by the older and better known men) and the American College of Surgeons, at its annual meetings, has programs given almost entirely by the well known surgeons except for brief clinical presentations by the local men. A particular young man therefore may have an opportunity only once in several years to present his work to that organization. About 25 years ago a group of young physicians, in protest against a similar situation regarding the American Association of Physicians, organized a very active separate group known as the American Society for Clinical Investigation. The American Physiological Society and the various societies which meet with it have recognized for years the desirability of giving the younger men opportunities. As a result of that policy and by means of sectional meetings those societies now have programs of over 1,000 papers. But the important point is that the young active workers in those fields can easily get a hearing before a national organization. We certainly do not need or desire any more surgical societies in this country. But it might be possible to reorganize this Association in some manner which would make up for the existing deficiency in surgery in this regard and yet provide for a preservation of its time-honored conservative traditions.

DOCTOR GROSS I should think it would be well worth while for this Association to see what it could do about that important matter. It seems to me important to avoid even a suspicion of stodginess. But, Mr. President, what steps have been taken by this Association in regard to the training of the young surgeon?

THE PRESIDENT I can tell you of some accomplishment in that direction, Doctor Gross Two years ago, under the able leadership of Doctor Archibald, who was then president, a symposium on the training of the surgeon was held at a meeting of the Association Two points were emphasized One was that some machinery should be set up whereby the public, both medical and lay, should be able to distinguish the trained and competent surgeon from the incompetent, and the other was that more facilities should be created for the adequate training of the young surgeon As a result of the discussion steps were taken to organize an American Board of Surgery which would certify competent surgeons Certain older men who were already known to be competent were to be given certificates as Founders without examination The younger men, and in the future all who apply, were to be given certificates only after fulfilling certain rather rigid requirements of training and after passing a stiff examination In addition, through this Board, aid was to be solicited of both the American Medical Association and the American College of Surgeons in the creation of a joint council to increase the facilities for the proper training of surgeons in various hospitals in which suitable organizations for that purpose could be established I am pleased to tell you that a Board of 13 members, representing various established surgical organizations, is now actively at work It has been received with enthusiasm, and its Founders Group numbers today 325 members Its first examination will be held next September

DOCTOR GROSS Is it the intention of the Board, Mr President, to ask hospital boards of trustees to appoint only certificated surgeons to their staffs? Also does the Board contemplate any pressure or persuasion to have legislation enacted of a sort which will allow only certificated surgeons to practice surgery?

THE PRESIDENT No, Doctor Gross, the Board feels that the most certain way to kill this promising movement would be to have an impression spread over the country that it proposes to exercise any dictatorship or any interference with the liberty of any individual in the practice of surgery The spirit of the whole movement must be free from the idea of compulsion or of force The thought must be uppermost that it is a privilege and an honor to have one of the certificates, but not that the Board shall have the right to say who shall and who shall not be allowed to practice surgery

DOCTOR GROSS I am much pleased to hear about the American Board of Surgery and particularly delighted to know that it had its origin in this Association That is the sort of activity which I should regard as peculiarly the function of the American Surgical Association I wish the Association were interesting itself in more of the matters which we have discussed Well, Mr President, I want to thank you again for inviting me here this morning I have enjoyed the discussion and I wish the Association continued prosperity I am sorry that I must leave now I have a consultation early this afternoon

with Galen about Hippocrates. The old gentleman fell down last night coming home from a party and dislocated his halo. We are going to try to reduce it. In view of the difficulty of the return journey from New York I think I ought to get an early start. Good-bye, Mr. President.

THE PRESIDENT. Good-bye, Doctor Gross. All of us would be glad to help you with Hippocrates, but I fear that none of us has had any experience in reducing dislocated halos. Nor do I know of any specialists in that field, not members of this Association.

DISCUSSION.—DR. ELLIOTT CUTLER (Boston). I should like to speak for a moment, Mr. President, to thank you for your point of view, and to signify my entire agreement in the suggestions which you have made for improving our meetings and enlarging the activities of our Society.

All the matters which you have brought forward I am sure are close to the thoughts of a large percentage of the Fellows. It is extraordinary indeed that we have not tackled the problem more intensively and more thoroughly. I should like to propose that when a committee does look into this matter, they consider the proposal that more papers can be heard each year in the same period by cutting down to ten minutes the time devoted to each paper. A speaker can tell in that period of time the story he wishes to put across, thereby considerably increasing the number of papers. That has been done by the Association of American Physicians and other societies with a great deal of success and has made their meetings, I am sure, much more attractive.

MEMBERS OF THE ASSOCIATION. If you feel that the Association can profit from the remarks and suggestions of Dr. Gross, may I ask that a motion be made to appoint a committee to investigate the reorganization of the Association and to make such recommendations as it may care to at the regular meeting next year.

INTRACRANIAL PRESSURE WITHOUT BRAIN TUMOR

DIAGNOSIS AND TREATMENT

WALTER E DANDY, M D

BALTIMORE, MD

DURING the past seven years there have gradually accumulated 22 cases in each of which the signs and symptoms of intracranial pressure have been indubitable, and yet in none has there been an intracranial tumor or a space occupying lesion of any kind. Almost without exception a clinical diagnosis of an unlocalized brain tumor has been made, but by ventriculography a brain tumor has been excluded. All of these patients have complained of headache, most of them of nausea, vomiting, diplopia, dizziness, many of loss of vision, and objectively in every instance there have been bilateral papilledema and usually hemorrhages in one or both eyegrounds to indicate, or at least strongly suggest, that intracranial pressure of advanced degree was present. And in each case the intracranial pressure has been objectively demonstrated and usually actually measured by ventricular or lumbar punctures, and finally the subsequent demonstration of pressure over a period of months or years is merely a matter of inspecting the site of the subtemporal decompression to which most of these patients were subjected for treatment. The increased intracranial pressure may last only a few months, but it at times persists five to seven years, and doubtless longer. Curiously, the decompression is almost never consistently at its maximum fullness but is intermittent, and the pressure may come and go with surprising rapidity—from one extreme to the other in a few minutes. The cause of the sudden changes—indeed the cause of the increased pressure at all—is unknown.

HISTORIES OF THE CASES CONSIDERED

Case 1—Unit 11820 B O F Age 21 April 27 to May 14, 1927

Complaints—Headache and failing vision

Present Illness—Three months ago patient awoke from her sleep smelling illuminating gas. She tried to get up, but fell and struck the back of her head. She vomited that day and the following day. There has been headache in the occipital region since that time and she ascribes it to the injury of the head. The headache is worse in the morning. Since the original episode her vision has been failing, objects are indistinct and there are spots before her eyes. When she tries to read she becomes dizzy and the print melts away. Two weeks ago she thought she staggered, but this lasted only for a day.

Examination—Patient is a normal appearing young woman of 21. There is papilledema of both eyegrounds, measuring two and one-half diopters on each side. There are several large hemorrhages alongside both disks (Fig 1). Visual acuity is 20/15 in each eye. Visual fields are normal.

Trephine and Air Injection—April 30, 1927. Fluid spurted under pressure. The ventriculograms, however, were entirely normal. Wassermann of the cerebrospinal fluid was negative.

Operation—Right subtemporal decompression, May 6, 1927. The dura was quite

tight and the brain bulged markedly through the bony defect. No note was made concerning the amount of fluid obtained at the operation.

Subsequent Course—Patient was not seen again until November, 1936, at which time the decompression was soft and not bulging, however, it was not sunken. She says it has always varied, occasionally being prominent and fairly tense, and at other times sunken. This difference was particularly noticeable in the first two or three years following the operation, but recently the site of the decompression has not become full or tense.

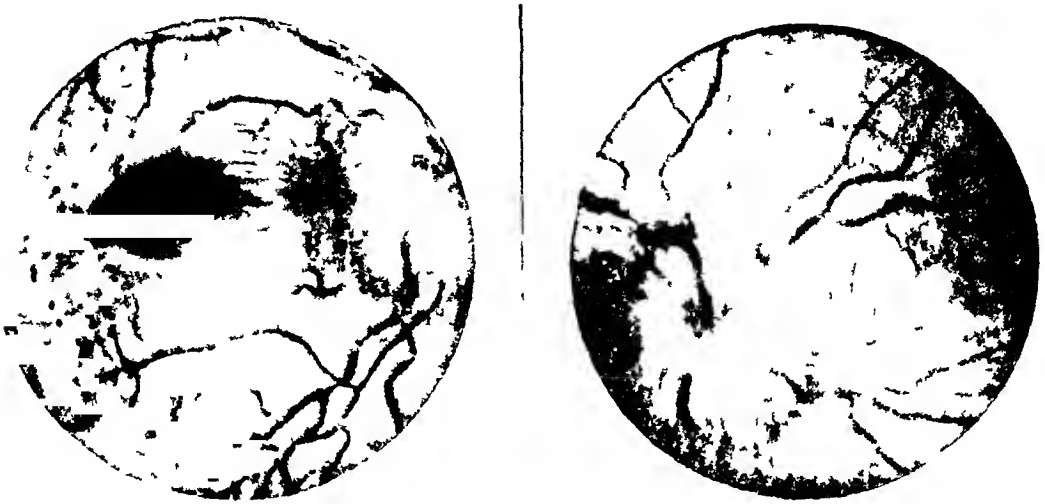


FIG. 1.—Eye grounds in Case I showing numerous hemorrhages, fulness and tortuosity of veins and obliteration of the disks.

Case 2—Unit 27949 V R F Age 27 November 12 to November 22, 1929
Complaints—Headaches and failing vision

Present Illness—Patient was perfectly well in every way until two years ago when she awakened one morning with a severe occipital headache, nausea and vomiting varying from once a month to two or three times a week. For the past 18 months the associated nausea and vomiting have disappeared entirely. Seven months ago an ophthalmologist found bilateral choked disks. For the past six months there have been progressive visual disturbances, at times there are spells of momentary blindness which she thinks are more likely to develop when she has been exposed to a bright light. At times she has noticed a narrowing of the field of vision to such an extent that it appeared to her as though she were looking through a key hole. This has been more progressive in the right eye. Between attacks of disturbed vision the eyesight is clear. Her eyes ache at times and there may be flashes of light when she closes her eyes, particularly when she is facing a bright light. There has been a buzzing in the ears at times, also noise like escaping steam. Her friends have told her that she staggers when she walks. There have been three or four spells of numbness in the right side of the face, sharply down the midline, these last for an hour or more, after which the normal sensation returns.

Examination—Bilateral papilledema of three diopters in the right eye and two diopters in the left. There are numerous large hemorrhages in and about the left disk. The visual acuity is 20/20 in the right eye and 20/30+ in the left. The blind spot is about four times its normal size in each field of vision. At one time a little hypo-esthesia was disclosed in the right trigeminal area, at other times this could not be found. There are no other positive neurologic findings. Her Romberg is negative, despite her history of staggering gait. The blood Wassermann was negative.

Trephine and Air Injection—November 15, 1929. The left ventricle was tapped. Fluid spurted under great pressure and stopped abruptly when about 10 cc had escaped. An equal amount of air was replaced. It was necessary to use pressure to force the air

into the ventricle. The ventricular system was small and perfectly normal in every way. The third ventricle was upright and in the midline.

Operation—A right subtemporal decompression was performed, under avertin anesthesia, immediately after the ventriculograms had been interpreted. The dura was exceedingly tense, so much so that we were fearful of the cortical rupturing in opening it. The descending horn of the ventricle was tapped and some air and fluid escaped, reducing the pressure to a point where the dura could be opened safely. The brain bulged almost to the maximum degree. There was very little fluid on the surface of the brain. Because of the great tension of the brain it was not possible to close the temporal fascia.

Examination of the Cerebrospinal Fluid—Eight cells, all lymphocytes, globulin negative, Wassermann negative.

Postoperative Course—Uneventful. Decompression remained full and fairly tense during her stay in the hospital. She has not been seen since. The following report was contained in a letter received December 14, 1934, five years after the operation: "It was about a year and a half after the operation before I could walk without staggering, although this is the first time I have ever admitted it, and from that time on I got much better. The lump on my head remained about the same until last winter when it went down to almost normal and has since remained unchanged. I get very few headaches and usually know the reason. I cannot stoop over much, or keep going too long without paying with a headache. However, I am really just fine and feel great. My eyes do not bother me at all. Have gained in weight—present weight 150 lbs."

Case 3—Unit 29509 M C M Age 45 February 13 to March 1, 1930

Complaints—Dizzy spells and drowsiness.

Present Illness—Ten months ago patient noticed a tendency to become drowsy. He would fall asleep when reading or sitting quietly, had a tendency to mix his words when he was talking, and he has had many spells in which both arms and legs would drop limp at his sides and he would be unable to talk. This would last from one to five minutes. Consciousness was not lost. There were no convulsions. He had no headaches. Diplopia has been present at times.

Examination—Patient is a well developed, strong looking man. Blood pressure 120/80. The neurologic examination is negative except for a low grade papilledema in each disk, there are no hemorrhages.

Trephine and Air Injection—February 18, 1930. Fifteen cubic centimeters of fluid were removed under great pressure. An equal amount of air was injected. The ventricular system was normal. The ventricular fluid showed no cells, no Pandy, negative Wassermann. Patient had a bradycardia at the time of his admission. During the next 48 hours he was somewhat stuporous, with a pulse running around 38 and 40.

Operation—February 18, 1930. The left hemisphere was explored because of the history of weakness on the right side and difficulty in speech. There was moderately increased pressure, but the surface of the brain everywhere looked normal. The bone flap was removed for a decompression. The decompression bulged markedly at the time of his discharge from the hospital.

Case 4—Unit 42619 A C F Age 42 April 5 to May 12, 1932

Complaints—Dizziness, headache and double vision.

Past History—Patient has always been extremely constipated. Because her basal metabolism was inconsistently low, ranging between -10 and -30 , for the past nine years she has been taking 1 to 3 gr. of thyroid extract daily.

Present Illness—Eight months ago she began getting dizzy when changing from a sitting to a recumbent position, or vice versa, also when turning the head from side to side, and more especially when she leaned forward. This was during a very hot summer. At times when leaning forward there was momentary blurring of vision. A month later a terrific right side hemiparesis lasted for an hour. During this time the vision was quite blurred and she was very dizzy, this attack began when she suddenly changed her position in bed. A month later or five months ago, diplopia developed and the dizzy spells

became so severe on changing position that she became frightened and was unwilling to lean forward to pick up anything. This condition remained essentially unchanged until a month ago when several more severe right sided headaches developed, the pain was more in the occipital region. There was a little nausea but no vomiting. Curiously, when the dizziness is on, it and the blurred vision can frequently be made to disappear instantly by throwing the head backward.

During the past two weeks there have been flushing spells, so severe that she feels that her face is burning up. She never had a keen sense of smell, but it has been worse in the past few years, and more so in the past few months.

Examination—Patient is a brilliant, normal looking woman, without nervous tendencies. Blood pressure 112/76. Basal metabolism -17. Both disks are swollen about four diopters. There are small hemorrhages about both disks. The visual fields and visual acuity are normal. Except for diminution of the sense of smell there are no other positive neurologic findings.



FIG. 2—Lateral and anteroposterior views of ventriculograms of one of these patients showing small symmetrical ventricles but no displacement. Given papilledema and intracranial pressure a tumor can be eliminated.

Cerebral Pneumography—A ventricular air injection was attempted but neither lateral ventricle could be reached. A spinal air injection was then performed under gas anesthesia. Fluid spurted under pressure. In view of the type of anesthesia one could not be certain that the pressure was not due to the anesthetic. Seventy-five cubic centimeters of fluid were removed, this exhausted the cerebrospinal fluid. An equal amount of air was injected. The ventricular system was small but normal in every way (Fig. 2).

Five days later, without an anesthetic, a lumbar puncture was performed. The pressure was 300 Mm. of water. The fluid was clear, contained four cells, negative globulin and negative Wassermann.

Since the ventriculograms showed a normal ventricular system, a tumor could be excluded. The interpretation, therefore, was that there was intracranial pressure of undetermined cause.

Operation—April 18, 1932. Under avertin anesthesia a second spinal air injection was done because we were still apprehensive that there might possibly be metastatic nodules which could so easily escape detection by an air injection, or perhaps even a tumor of the olfactory groove. Again the ventricular system was well filled and perfectly normal.

A right subtemporal decompression was then performed. Much to our surprise the brain was sunken beneath the dura. It was quite clear, therefore, that we were dealing

with a condition in which there were marked variations in the intracranial pressure. It is also worthy of note that there was no excess of fluid on the surface of the brain.

The postoperative course was uneventful. During her subsequent stay of three weeks in the hospital, the decompression remained, for the most part, full and tense, although there were times when it was quite flat and soft. Her diplopia and dizziness gradually diminished and had practically disappeared at this time. Up to the present time, five years later, neither the diplopia nor dizziness has ever reappeared. Her eyegrounds were found to be normal when examined a few months after her return home, and they have remained normal to date. The vision has been entirely normal. The decompression is still tense at times and it may be just as hard and tense as it was at the time of her operation five years ago. Perhaps more than half of the time it is soft and flat. She is well in every way and leads a very active life with many social activities (May 1, 1937).

I have been particularly eager to determine what may cause the rise and fall of the decompression, but on the whole have been quite unsuccessful. The pressure does appear to rise with any excitement, although this is not always true. A relationship with her obstinate constipation cannot be established, nor does the intake or restriction of fluid materially change it. She suffers no inconvenience whatever. There have been four or five convulsions during the past five years, none were present before. Since there is nothing connected with the air injections or decompression that could cause the convulsions, it has been assumed that they are in no way related to the intracranial condition that is responsible for the increased pressure. On the other hand, she is the only patient in the series who has had a convulsion subsequent to operation.

Case 5—Unit 37125 B P F Age 23 May 16 to 22, 1931, and again May 9 to 18, 1932

Complaint—Impairment of vision

Present Illness—Eight months ago patient became totally blind when changing from a recumbent to a sitting position. For the following six weeks the visual loss recurred several times a day. She is quite certain that shifting to other positions did not produce the same effect. Six months ago there were attacks suggesting right homonymous hemianopsia. Objects would disappear in the right half of her field. She had 100 or more such attacks during a day. Her eyes were then examined but nothing abnormal was found. Owing to the continuance of the same symptoms, a lumbar puncture was performed six weeks ago by Doctor Colella of Johnson City, N. Y. Fluid was said not to have been under pressure, although it was not measured. There was one cell and no globulin.

Five weeks ago headaches appeared in both frontal regions, these would last for two or three hours and disappear during sleep, they were throbbing and pounding in character. There had been nausea with the headaches, but no vomiting. In recent weeks the attacks of momentary blindness have come only in the right eye.

At the age of 14 or 15 (eight or nine years ago) she had some spells in which she could not get her breath. There is said to have been stertorous breathing. She could not talk, but understood what was said to her. These spells lasted about one-half hour and occurred once or twice a month. There were severe bifrontal headaches for about two hours after each attack.

Examination—She is considerably over weight, weighing 150 pounds. At the age of 16 she weighed 192 pounds and two months ago, 170 pounds. The present reduction in weight has occurred without dieting. The neurologic examination reveals only one finding, namely, papilledema measuring three diopters in the right eye, and one diopter in the left. The veins are full and slightly tortuous. There are no hemorrhages in either eyeground. The visual acuity is 20/20 in the right eye and 20/15 in the left. The visual fields are normal. The blind spot in the right eye is enlarged to about three times its normal size, on the left it is normal.

Trephine and Air Injection—May 19, 1931. Both ventricles were tapped. Fluid spurted under great pressure, then stopped abruptly. About 7 cc of air were injected.

into each ventricle. Pressure was required to inject the air. The ventriculograms were entirely normal.

Subsequent Course—Since she could be carefully followed at home she returned, hoping the condition might clear spontaneously. Her blind spells decreased in number but still remained. Her headaches were improved for some time, but again reappeared. She was again having attacks similar to those she had had at the age of 14 or 15, and which she now recognized as being hysterical. Four months later a spinal puncture was performed, the pressure was 250 Mm.

She was again admitted to the hospital, May 9, 1932. Her papilledema now measured only one and one-half diopters in the right eye and one diopter in the left. The visual acuity was 20/20 in each eye, the disks were definitely paler than before. Lumbar puncture on two successive days registered 300 and then 400 Mm. of water.

On May 10, 1932, air was again injected into the lateral ventricles, which were, as previously determined, small and apparently normal. This time there were 16 mononuclear cells in the spinal fluid.

Operation—May 10, 1932. A right subtemporal decompression was performed. The brain was very tense and bulged greatly but did not rupture when the dura was opened. There was no excess of fluid on the surface.

She returned for observation June 2, 1932, and stated that her headaches were less frequent and less severe. Two days after returning home her right arm and leg began to jerk occasionally and she could not control them so well. She says it caused her to break many dishes. She had another blind spell three days ago, on this occasion only the right eye was affected. The decompression was soft most of the time while at home, but has again become quite bulging and tense. Three days ago both legs became weak and she developed a stumbling gait. There still appears to be some slight motor weakness in the right hand and the finer movements are less well performed. There is no tremor, no ataxia and no astereognosis. She walks with a rather broad base, but there is no definite staggering, and her Romberg is negative.

She was again seen March 19, 1937. The decompression still protruded slightly, but it was quite soft. She says it does get more tense at times. Her vision is normal. Her blind spells have ceased. The disturbances with the legs, and particularly the right leg, and also the right arm, have cleared. She is quite nervous and has become addicted to drugs.

Case 6—Unit 43567 C B F Age 46 May 28 to June 11, 1932

Complaints—Headache and buzzing in the right ear.

Present Illness—Began four months ago when she developed inconstant, dull, aching pain in the region of the right mastoid. There was also pain in the right frontal region, and a little tinnitus in the right ear. Dizziness has been present at times.

Examination—Patient looks well, though somewhat overweight. Blood pressure 128/80. The neurologic examination is negative, except for papilledema of four diopters in each disk, there are numerous hemorrhages on both sides. Vision and visual fields are normal. Roentgenologic examination of the head is negative.

Trephine and Air Injection—May 31, 1932. Fifteen cubic centimeters of fluid were removed from the right ventricle and an equal amount of air injected. The ventricular system was normal. The cerebrospinal fluid contained two cells and no globulin, Wassermann was negative. A spinal puncture was performed three days later, pressure was 550 Mm. of water.

Operation—June 3, 1932. A right subtemporal decompression was performed. The brain was under great pressure and bulged almost to the maximum degree. The decompression was full and tense at the time of her discharge from the hospital.

Case 7—Unit 45653 A R F Age 34 October 3 to 25, 1932

Complaint—Headaches.

Present Illness—Eight months ago patient had an attack of headache lasting three days, it was continuous day and night and was accompanied by nausea and vomiting.

The headache was more in the right frontal region than elsewhere, but it was also generalized. At the same time there was marked photophobia. A month later there was a similar attack lasting for five days. In the interim she had been well. Two months later a third attack lasted three weeks. She vomited three or four times a day. Two weeks later a fourth attack was accompanied by stiffness and soreness in the neck and a sensation of pins and needles along the inner sides of both arms. The attacks since recurred about once a month. On her visit to the Johns Hopkins Dispensary during the past month, bilateral papilledema was discovered.

Examination—A large, obese woman, age 34. Blood pressure 110/80, pulse 82, blood Wassermann negative. The neurologic examination reveals but one finding, namely, papilledema of about two diopters in each eye. The veins are full and tortuous but there are no hemorrhages. Visual acuity and visual fields are normal.

Trephine and An Injection—October 5, 1932. Twelve cubic centimeters of air were injected into the right ventricle. Fluid spurted under pressure. The ventriculograms showed a normal ventricular system. The fluid contained four mononuclear cells, no globulin. Four days later a lumbar puncture was performed. The pressure was 330 Mm of water. The Queckenstedt test was normal. There was a response of over 20 Mm on compression of each jugular, and 40 Mm on compression of both.

Operation—October 15, 1932. A right subtemporal decompression was performed. The dura was quite tense. A large amount of fluid escaped under pressure when the dura was opened, the fluid was in the subarachnoid space. After the fluid had escaped, the brain still bulged through the bony defect.

Subsequent Course—The decompression was usually full and tense, but on many occasions was soft and sunken. When I saw her four months after the operation the decompression was soft, but protruding, she said that on the day preceding it had been so tight and hard that she could not lie upon it.

Her headaches continue, but with much less severity and are practically confined to the right side. These headaches come on an average of once a week and last for two or three days, they are sharp, like a knife thrust. There has been some dizziness during these attacks and some ringing in the right ear. She is quite sure that the headaches have no relationship to the tight decompression. She says they come just as much when the decompression is soft. Both disks are normal in outline and color, and the veins are of normal size.

Hoping to relieve the headaches, I removed the stellate ganglion. She went for three months without a headache, but they again recurred and were of the same type. She is quite nervous, cannot sleep at night and has bad dreams. How much her headaches are genuine and how much functional is difficult to determine.

At the time of my examination a year ago (May, 1936), the decompression was full and very tense.

Case 8—Unit 46919 S H F Age 32 December 15, 1932, to January 2, 1933

Complaints—Headaches, blurring of vision, colored spots before the eyes, double vision.

Past History—Ovarian tumor was removed three years ago. Prior to this operation she had lost 40 pounds in weight, this has been regained. Her periods again became regular after the operation and have since been normal.

Present Illness—Soon after her ovarian operation three years ago, occasional dull headaches began, they were more in the frontal and occipital regions, were not especially severe and occurred quite irregularly, at times they might come every two or three days, and again would not reappear for two or three months. Four months ago she began to tire easily, felt badly, and found it difficult to do her house work. Her condition was worse at the menstrual period, at which time there was a dull ache in the right side of her abdomen.

Five weeks ago a sudden, sharp pain developed in the back of the head, perhaps more severe on the left side, this pain has been continuous to date and is worse at night. There

have been diplopia and black spots in front of her eyes. Three weeks ago her vision was found to be failing, particularly in the right eye, and a week later she was unable to see anything with this eye. There was vomiting on one occasion, three weeks ago. There was also a transient numbness in the left arm at that time. She staggered for a time and had ringing in the right ear. Four days ago, for no apparent reason, the vision returned in the right eye so that she had a definite field of vision, including colors.

Examination—Patient is a large woman, considerably overweight (present weight 190 pounds). There is swelling of four diopters in each disk. There are numerous hemorrhages in both eyegrounds, the veins are full and tortuous. The visual acuity is 20/50+ in the right and 20/20 in the left eye, the field of vision is normal in the left and about one-fifth of the normal in the right. The neurologic examination otherwise is entirely negative. Vaginal examination reveals no signs of a tumor recurring from her operation of three years ago.

Tentative Diagnosis—It was clear that patient had severe grade of intracranial pressure. The possibility of metastases from a malignant abdominal lesion was strongly considered.

Trephine and Air Injection—December 20, 1932. Twenty cubic centimeters of fluid were removed from the right ventricle and 10 cc of air injected. There were two cells in the fluid. I could not be sure about the degree of pressure. A lumbar puncture was performed four days later and the pressure registered 320 Mm of water. The Queckenstedt test was normal, there was no globulin, Wassermann negative.

Operation—December 24, 1932. A right subtemporal decompression was performed. A fair amount of fluid on the surface of the brain, which was very tense, but when the fluid had been evacuated the brain bulged but slightly.

Subsequent Course—Letter received June 4, 1936 (three and one-half years after operation). Patient is well and does housework for family of six. Her vision is good in the left eye, still defective in the right. She has no headaches. The decompression swells at times, especially when tired, and goes down quickly when she rests.

Case 9—Unit 60526 E V F Age 9½ February 8 to 25, 1935

Complaints—Headaches and vomiting.

Present Illness—Five months ago generalized headaches appeared, which occurred in spells and quite frequently. Two and one-half months ago she fell off her horse, struck her left jaw, was not unconscious, but was somewhat dizzy. She rode the horse home, vomited that night after dinner but seemed her usual self the next day. Her parents thought the headaches became more frequent following this injury. Two months ago one of the episodes of headache and vomiting lasted five days, but following this she was well for nearly a month, when the headaches again returned, accompanied by vomiting. At this time she had an attack that lasted eight days. Her urine was said to have contained acetone and her NPN was elevated to 68 mg. Four days later the blood chemistry was within its normal limits. About this time diplopia was first noted and an examination of the fundi revealed bilateral papilledema. Ten days ago a lumbar puncture was performed at her home in Mexico City, xanthochromic fluid was said to have been recovered, Pandy was positive, four cells. Her physician also noted paralysis of the left external rectus muscle.

During this time the headaches continued. There was numbness of the hands at times, during the past month. The headaches have never been localized. Appetite has been rather poor during the past month. There has been no disturbance in gait, no convulsions and no change in personality.

Examination—An undernourished girl is in bed because she feels ill. Blood pressure 120/70, pulse 90 to 100. Tuberculin test (0.1 mg) was markedly positive.

The neurologic examination is negative, except for papilledema of three diopters in each eye. There are several hemorrhages in the right disk, the veins are full and tortuous. The appearance of the left disk is essentially similar, except that there are no

hemorrhages The visual acuity is 20/50 in each eye Visual fields are normal There are no scotomata The abducens palsy has disappeared

Operation—An air injection was performed February 8, 1935 The ventricular system was perhaps a trifle enlarged, although within the limits of normal There did not appear to be any pressure, although this could not be definitely determined The ventricular fluid contained no cells and no globulin A guinea-pig which was injected with this fluid later died of tuberculosis

One week later a spinal puncture was made without anesthesia The pressure registered 500 Mm of water There were two cells in the spinal fluid, Pandy was negative A guinea-pig was also injected with this fluid and eventually died of tuberculosis

A right subtemporal decompression was performed February 15, 1935 The dura was very tense, when opened the fluid poured out in tremendous quantities, much as obtains in fractures of the skull We looked carefully for evidence of tuberculosis, but none could be found Even with the escape of the tremendous amount of fluid, and the loss of 85 cc of fluid from the lumbar puncture immediately preceding the anesthetic, the brain was now only flush with the dura After operation the decompression was never tense She left the hospital February 25, 1935, quite free from symptoms

Subsequent Course—A letter received from the father March 12, 1937, two years after operation, stated that the patient had been entirely free from symptoms up to that date and was well in every way Her physician reported normal eyegrounds and normal vision We had been apprehensive because two guinea-pigs had died of tuberculosis

Case 10—Unit 66287 A M M Age 44 November 22 to December 9, 1935

Complaints—Headaches and dizzy spells

Present Illness—Dull headaches have been present in the right frontal region for the past eight months, they come in spells lasting several hours and occur almost daily They have not become more severe nor more frequent On two occasions he has had a feeling of giddiness, once so severe that he fell

Examination—Patient is a large, well nourished man, seemingly in good health The physical examination is negative Blood pressure 118/64 The neurologic examination is negative except for papilledema of three diopters in each eye There are numerous small hemorrhages on both sides Vision is normal Roentgenologic examination of the head is normal

Trephine and An Injection—November 26, 1935 Fluid spurted under high pressure but only 55 cc of fluid were obtainable Ten cubic centimeters of air were injected The ventricular system was normal The cerebrospinal fluid was not examined

Operation—November 26, 1935 Immediately after the ventriculograms were read, a right subtemporal decompression was performed The brain was under tremendous pressure Despite the release of a considerable quantity of fluid, the brain still protruded markedly

Subsequent Course—The decompression was full and tense at the time of his discharge from the hospital

I examined the patient again March 17, 1937, 16 months after the operation He was quite well and plays golf The decompression was full and tense He says it is that way very much of the time but is also frequently flat When the decompression is very tense there is a little headache and the eyes feel as though they were being pushed out, at these times there are colored rings about both eyes The vision and visual fields are normal, the disks are sharply defined and the veins of normal appearance He says reading, talking and nervousness quickly cause the decompression to become tense and full—the time required for it to change from one extreme to the other is less than two minutes He also thinks the decompression becomes more tense when he is constipated

Case 11—Unit 66817 R H F Age 41 December 20 to 30, 1935

Complaint—Blurring of vision in the left eye

Present Illness—One and one-half years ago an intermittent blowing sound developed in the right ear This was synchronous with the heart beat She found by lying in

certain positions or by holding the upper right side of her neck with her hand the noise would stop. The noise occurred irregularly, and was not sufficiently disturbing to keep her awake. Three months ago blurring of vision was noted in the left eye. This was not associated with any other symptoms. She is quite certain that she has had no headache, and aside from loss of vision there have been no other disturbances.

Examination—Patient is a well nourished, normal looking woman, a little overweight. Blood Wassermann negative. Blood pressure 140/76. Roentgenologic examinations of the head are negative. In each fundus there is papilledema of three diopters, large hemorrhages cover both eyegrounds. Visual acuity is 20/20 in the right eye, 20/40 in the left. Visual fields are normal. The blind spots are slightly enlarged.

Trephine and An Injection—December 21, 1935. Fluid spurted under great pressure, only a few cubic centimeters of ventricular fluid escaped. Ten cubic centimeters of air were injected. The ventricular system was normal in every way, but both lateral ventricles were markedly undersized.

Operation—A right subtemporal decompression was performed the same day. The dura was exceedingly tense and the brain bulged greatly when it was opened. However, there was quite a free flow of fluid from the subarachnoid space and before the operation was concluded the brain was flush with the level of the dura, but not beneath it. There were no signs of abnormalities in the brain. The patient was discharged December 30, 1935, the decompression was full and tense.

Subsequent Course—A letter from her husband February 4, 1937 (15 months after operation), states "Mrs. H. feels fine. She doesn't sleep very well at night. The bump on her head where she was operated seems swollen quite a bit, but otherwise she is in fine health." Visual acuity and visual fields taken by Dr. Walter R. Parker, of Detroit, were normal.

Case 12—Unit 67385 S W F Age 13 January 21 to February 16, 1936

Complaints—Failing vision, diplopia and headache.

Present Illness—Seven months ago pain developed in her left hip causing her to limp. The pain progressed steadily for three months when she was no longer able to walk. Roentgenograms were taken and were said to have been negative. A month later a second roentgenologic examination revealed an abnormality about the epiphysis at the head of the femur and atrophy of its neck. The leg was placed in a plaster spica. The pain immediately disappeared. She felt better, ate heartily and gained some weight. A month later, *ic*, two months ago, she had an attack of vomiting. One month later, *ic*, one month ago, she complained of dizziness and headache over both eyes. Within a week her eyesight became blurred, there was double vision and the headache had become much more severe. It was then located in the occipital as well as the frontal region. There were pain and stiffness in the neck. Vomiting became more severe, occurring several times a day. Three weeks ago the plaster spica was removed and an appendicectomy performed because of the vomiting. There was no upset following the operation, and although her headache continued, the vomiting ceased. One week ago her vision had become so poor that she could only recognize light with the left eye. She was still able to read with the right eye. For the past three or four weeks there have been attacks of numbness in the right leg (not the leg in the spica).

Examination—Patient is a sallow, fairly well nourished, young girl suffering severely with headache. Temperature normal, pulse 110, respirations 24, blood pressure 120, WBC 7,800. There is a definite cracked-pot sound (Macewen's sign) on tapping the frontoparietal suture line. Moreover, roentgenologic examination showed separation of sutures—unusual at the age of 13, and indicative of an extreme degree of intracranial pressure. There is only light perception in the left eye. She can read ordinary print with the right eye. Being bedfast and in a plaster spica, a more detailed eye examination is not possible. There is papilledema of five to six diopters in the right eye, two to three diopters in the left (the blind eye). The disk and surrounding retina are filled with large flame-like hemorrhages, these are more pronounced on the right side. There is

weakness of the external rectus muscle on the left, but the parents say this has always been present. The knee jerks on the right could not be elicited, the left leg is in a plaster spica. Babinski is negative, no clonus.

Diagnosis—Although I had suspected a tuberculous hip and a metastatic infection of the brain, Dr. George Bennett, who saw her with me, excluded tuberculosis from the study of the roentgenograms. The coexistence of the two lesions made us suspect a relationship between the two, but the only positive finding in the hip was the epiphyseal separation and atrophy of the neck and upper part of the shaft. There was no positive infective process.

Trephine and Air Injection—January 22, 1936. The right ventricle was tapped. Fluid spurted out under tremendous pressure—at least at a distance of three feet. About 15 cc. of fluid escaped and then the flow shut down abruptly. Ten cubic centimeters of air were injected under pressure to replace the fluid. The ventriculogram showed a perfectly normal ventricular system. The fluid showed four cells, all lymphocytes. A guinea-pig was inoculated with the fluid, because of the suspicion of tuberculosis, it had no effect upon the animal.

A right subtemporal decompression was performed immediately after the ventriculograms had been interpreted. The dura was exceedingly tense. A small nick was made in the dura, hoping that fluid might be encountered and thus reduce the terrific tension. A large amount of fluid did escape, but it seemed to make little, if any, impression upon the tension of the dura. The dura was rapidly opened but the pressure was still so extreme that the cortex ruptured inferiorly. The intracranial pressure had just about reached its limit.

Following the operation the decompression was exceedingly tense. A spinal puncture on the third day after operation registered 460 Mm. of water, thus, in spite of the decompression. With this great pressure it looked as though the decompression would be futile. A lumbar puncture was performed on each of the following seven days, about 30 cc. of fluid being removed each time. On the eighth day after operation the spinal fluid pressure registered 350 Mm. The tension of the decompression gradually decreased during the next five days. On the fourteenth day the decompression was flat and the spinal fluid pressure measured 160 Mm. Patient remained in the hospital a week longer. The decompression remained perfectly flat throughout that time.

For a few days after operation patient was unable to see with either eye. As the pressure became less her vision returned and at the time of her discharge she was able to read fine print with the right eye, but the left eye still remained blind. Her general condition had changed entirely, her color was better, and she was very much more alert and active mentally.

Subsequent Course—When examined by me three months later, she was totally blind, had severe headaches, and the decompression was as full and as tense as it could possibly be. The left optic disk showed extreme optic atrophy with sharply defined disk and normal sized veins. The right had much the same appearance but slightly less advanced. It did not look as though vision could ever return. Within two weeks the decompression was again flat, and vision returned in the right eye. February 12, 1937, 13 months after operation, she was well, had had no more evidences of increased pressure, the decompression had remained soft, her vision was 20/70 in the right eye and there was a fairly normal field of vision. Her femur has healed and gives no trouble, there is no limp.

Case 13—Unit 69343. R. W. F. Age 31. July 8 to 20, 1936.

Complaints—Headache and blurred vision.

Past History—Aside from a chrome discharging ear on the left side since the age of nine, the past history is negative.

Present Illness—This is dated, by the patient, to an automobile accident five years ago. Since this time she has had occipital headaches, more recently they have become generalized. At times there is a feeling of giddiness and unsteadiness on her feet, but no

true vertigo At times there are spots before her eyes and the vision is blurred There has been no diplopia

Examination—Patient is a rather obese, well developed, healthy looking but highly nervous woman She does not appear ill Blood pressure is 124/76, blood Wassermann negative There is papilledema measuring two diopters in each disk There are a few small hemorrhages about each disk The visual fields and visual acuity are normal

Trephine and Air Injection—June 13, 1936 Both ventricles were small Ten cubic centimeters of fluid were removed from each ventricle and an equal amount of air injected The ventriculograms were negative The ventricular pressure could not be determined because the ventricles were too small The ventricular fluid showed three cells and a negative Pandy

Spinal Puncture—July 8, 1936 Pressure measured 430 Mm of water Fluid was clear, four cells, negative Pandy Wassermann negative

Operation—July 11, 1936 Decompression The dura was under high tension Fluid poured out in large amounts when the dura was opened Fluid was everywhere through the subarachnoid spaces When the fluid had ceased to flow the brain still bulged markedly

Subsequent Course—January 4, 1937, patient states swelling has disappeared

Case 14—Unit 71733 V D F Age 20 August 10 to 22, 1936

Complaint—Headache

Present Illness—Three years ago (April, 1933) severe generalized headaches developed An examination of her eyegrounds at that time revealed choking of the right disk She had no visual symptoms at that time in fact no symptoms except headache Two months later air was injected into her spine by her physician A year later she was seen by a neurologic surgeon who performed a ventricular air injection The ventricles were apparently normal She was blind for 24 hours following this procedure Since then she says her vision has not been as good as it was before She says there has been fever off and on during her illness of the past three years At one time she kept a record and found that her temperature rose to 100° or 101° F nearly every afternoon She has been examined for various infections, but nothing has ever been found Headache still remains the only symptom It remains essentially unchanged and is not localized

Examination—Patient is a normal appearing female, age 20 Her physical examination reveals no abnormalities Blood Wassermann negative Blood pressure normal Roentgenologic examination of the head is normal Neurologic examination reveals only bilateral papilledema This is of low grade in the left eye but there is an elevation of four diopters in the right There are no hemorrhages in the eyegrounds Her vision and visual fields are normal

Spinal Air Injection—August 14, 1936 Since a tumor was not regarded as a very strong probability, a spinal air injection was made The spinal pressure was 330 Mm of water One hundred cubic centimeters of fluid were removed and an equal amount of air injected The lateral ventricles were imperfectly filled and were very small but normally placed

Operation—August 14, 1936 A right subtemporal decompression was performed The brain was very tense and bulged through the dural defect, but there was no fluid on the surface of the brain

Case 15—Unit 74033 P W F Age 19 November 3 to 11, 1936

Complaints—Blurring of vision, double vision, headaches

Present Illness—Three months ago vision became blurred and distant objects were seen double Headaches began at the same time, they were generalized and appeared to begin and end in no particular region, they were somewhat worse at night There was no vomiting or vertigo

Examination—Blood pressure, 124/70 Wassermann negative Neurologic examination is entirely negative except for bilateral papilledema of two diopters and some diminution in visual acuity There are numerous hemorrhages about both disks The

visual fields are normal The visual acuity is 20/40 in each eye The blind spots are perhaps very slightly enlarged *Tentative Diagnosis* Brain tumor

A lumbar puncture was performed immediately before the air injection The pressure registered 530 Mm of water On account of the severe pressure, air was not injected by the spinal route

Trephine and Air Injection—November 4, 1936 Intracranial pressure was very high, the fluid spurting The ventricular system was entirely normal

Operation—A right subtemporal decompression was performed the same day The brain was very tense, and great quantities of fluid poured from the arachnoid when it was punctured At the time of closure the cortex bulged slightly

Subsequent Course—June 10, 1937 Patient states that the operative area swells when she lies down, at other times it is flat Her vision is good

Case 16—Unit 74464 BFS M Age 29 December 8 to 18, 1936

Complaints—Headaches and loss of vision

Family and Past Histories—History of syphilis Patient lost the left eye in an accident during childhood

Present Illness—Three years ago headaches began, they were in the occiput and behind both ears For six months the neck was stiff He then began vomiting and the headaches became intensified, subsequently subsiding During the past three months more or less constant dull frontal headaches have occurred For the past two months the vision in his left eye (only) has been impaired He also thinks he has staggered during this time, some dizziness, frequent vomiting, loss of 34 pounds in weight

Examination—Patient is a very much undernourished, ill looking man with sallow complexion He clearly shows the loss of 34 pounds in weight Blood Wassermann four plus Papilledema of two diopters in the left eye—the right has been removed There are no other positive neurologic findings

Trephine and Air Injection—December 9, 1936 The ventricular system was entirely normal Later the pressure of the spinal fluid measured 250 Mm of water, there were no cells, Pandy was positive and the Wassermann four plus

Right Subtemporal Decompression—December 11, 1936 Since patient had only one eye a decompression was made, even though the intracranial pressure was not greatly increased The brain bulged moderately, with a fair amount of fluid, after the evacuation of which the brain became flush with the dura The patient was discharged December 18, 1936

Letter May 18, 1937 Condition is essentially unchanged

Case 17—Unit 104829 A S M Age 44 April 19 to 29, 1937

Complaints—Pain in the back of the head and blurring of vision

Present Illness—Began three months ago when a severe pain developed in the lumbar region and radiated to the back of the head where a severe headache developed which persisted for two days During the time of the severe headache there was a numbness and tingling in his right foot and hand, but there was no loss of motor power One week ago he vomited on several occasions Nine days after the first attack a similar lumbar pain again developed which radiated to the head, this persisted for only one day but the back pain lasted for ten days, only during the past week has he been free of it Ten days ago diplopia developed but soon disappeared, it recurred several times during the following three days His vision has been blurred to such an extent that he has been unable to read fine print At the present time there is very little headache and this is not at all localized It is not intensified by change of position

Examination—Patient is a well developed, well nourished man Blood pressure 126/84, blood Wassermann negative There is bilateral papilledema of three diopters and numerous hemorrhages in both eye grounds, the veins are full and tortuous The visual fields are normal, but the visual acuity is reduced to 20/30 in each eye following correction by glasses Possibly there may be slight weakness of both external recti Roentgenologic examination of the head is negative

Ventricular An Injection—April 20, 1937 Fluid spurted under marked pressure Fifteen cubic centimeters of fluid were removed and an equal amount of air injected The ventricular system was normal

A spinal puncture was performed immediately and registered 480 Mm of water The fluid showed four cells, no globulin and negative Wassermann

Operation—A decompression was performed on the same day The brain was exceedingly tense There was quite a little fluid on the surface, enough to reduce the pressure so that finally the brain bulged but slightly beyond the cranial vault Patient was discharged from the hospital nine days later At the time of his discharge the decompression area bulged but slightly

Subsequent Course—Three weeks later the site of the decompression had suddenly become very full and tense He said before this it had not protruded This fulness and increased tension had been present for the preceding 48 hours

Case 18—Unit 103973 H B Colored F Age 29 April 28 to May 10, 1937

Complaint—Pain in the head

Present Illness—One year ago bifrontal headaches began, they also extended into the temporal region and were especially pronounced just back of the eyes They were intensified by bending over and on returning to the upright position For the past three weeks the headache has been very severe There has been slight diminution in visual acuity, but no diplopia There have been no other symptoms

Examination—Patient is a rather obese, but healthy looking colored woman The physical examination is entirely negative except for a slightly increased blood pressure which registers 150/90, three weeks previously, when taken in the dispensary, it was 170/100 Blood Wassermann negative Urine two plus albumin There is papilledema of two diopters in each fundus There are no hemorrhages The visual fields are normal, visual acuity 20/15 in each eye Roentgenograms of the head are negative

Ventricular An Injection—April 28, 1937 Entirely negative The ventricles were rather small

Spinal Puncture, May 3, 1937, registered 250 Mm of water The Queckenstedt test was negative on both sides The spinal fluid contained no cells and no globulin, Wassermann was negative

Operation—A right subtemporal decompression was performed May 5, 1937 The brain was very full and tense There was almost no fluid on the surface of the brain so that it bulged markedly at the time the temporal muscles were approximated

Case 19—Unit 27262 M G F Age 24 October 4 to 25, 1929

Complaint—Headache

Present Illness—Began two years ago with terrific headaches lasting a few hours and occurring every five or six days, they were mainly in the right frontal region Four months ago they became more severe and were present almost every day During the past month the headaches had been almost constant, but worse at night On two occasions the patient had vomited when the headache was especially severe There had been a little dizziness at times, particularly when the patient moved abruptly or stooped over

Examination—Patient is a large well nourished, well developed colored girl, age 24 Blood pressure 110/82, pulse 70 Blood Wassermann negative There is bilateral papilledema of four diopters, a little more marked on the left, and a few small hemorrhages at the disk margin on the left Her vision is normal

Trephine and An Injection—October 5, 1929 Fluid spurted under high pressure, but only a few cubic centimeters were obtained Ten cubic centimeters of air were injected under pressure Ventriculograms showed the ventricular system to be entirely normal There were three cells and no globulin in the ventricular fluid Wassermann negative

Operation—October 5, 1929 As the right ventricle was not as well filled as the left, and her headaches were definitely unilateral, we felt that if it were a tumor it would be on the right side Accordingly an exploration of the right hemisphere was made The brain was very tense, but there was fluid everywhere in the sulci, and when this was

evacuated and the ventricle tapped it was not difficult to close the dura. A decompression was not performed.

Subsequent Course—On October 22, 1929, 17 days after operation, another air injection was performed. Again the ventricular fluid was under high pressure and the ventriculograms again showed the ventricular system to be entirely normal. The patient was seen two months later, at which time the papilledema was still present, but less than when she was in the hospital. She was then free of headaches entirely. A letter April 1, 1936, says patient is normal in every way and vision is unaffected.

Case 20—Unit 65474 S M M Age 48 October 14 to November 23, 1935

Complaints—Headache and drowsiness

Past History—Negative, except that patient is said to have had attacks of kidney stone without hematuria.

Present Illness—Patient was first seen when he was comatose. He had right sided headaches for the past three weeks. When the headaches began he had suddenly become irrational. A spinal puncture was done at his home and a pressure of 300 Mm of water was reported. Following this he was somewhat improved. He was brought to a hospital in Baltimore where he again suddenly became drowsy, then unconscious. A lumbar puncture was done in another hospital, it measured 200 Mm and the fluid was said to have been xanthochromic.

A careful neurologic examination was made by Dr Irving Spear and was entirely negative. I saw him when he again passed into coma, at this time his pulse ranged between 60 and 70. I thought he had a brain tumor and advised ventriculography.

Trephine and Air Injection—October 14, 1935. Air injection showed definitely increased pressure, though it was not excessive and was not measured. Twenty-five cubic centimeters of fluid were removed and an equal amount of air injected. The ventricular system was entirely normal. As the fluid was somewhat bloody, a cell count and globulin examination were not made. During the next few days the patient became gradually more responsive, but was disoriented and had hallucinations. He had some pain in the right side of his head. Gradually he became quite normal again.

Nine days after the operation for ventriculography, he still complained of a little headache. A lumbar puncture was done and registered 160 Mm of water. The fluid was perfectly clear and there were no cells and no increased globulin.

On October 29, 1935, there suddenly developed a severe attack of auricular fibrillation with pulse deficit of 64, the heart beat was 144. Under treatment improvement began at once and the heart rate was soon normal, and remained so up to the time of his discharge. His wife then recalled that he had had a seemingly similar attack at the beginning of his present illness. Following this last attack his general condition was improved and he was seemingly quite normal in every way.

On October 31, 1935, another lumbar puncture was done. He was then having increased headaches and the ventricular pressure registered 230 Mm of water. The fluid showed 48 cells and a positive Pandy, but the fluid was blood tinged. The Wassermann reaction was normal. He had no more attacks of arrhythmia or hallucinations, and his headache disappeared. He left the hospital November 23, 1935.

It should be noted that although his eyegrounds were negative on admission, there was a definite papilledema of two diopters in each eye, and a single hemorrhage in the left eye, when examined on November 11, 1935.

In view of the fact that he was symptomatically so well, that his vision could be watched, and that his spinal pressure had not been high, it was not thought advisable to perform a decompression.

Subsequent Course—Five months later he wrote that he was quite well, except for some dizziness and pains in the head when active.

Case 21—Unit 67255 M D F Age 27 January 14 to 21, 1936

Complaint—Headache

Present Illness—Twelve days before admission patient was delivered of a full term

baby Throughout pregnancy and delivery nothing unusual happened Three days after confinement a sudden severe right frontal headache developed, which soon became generalized, although it remained more intense on the right side On the following day she vomited many times, and on the next day there was intense nausea but no vomiting The headaches persisted, though they were less severe On the seventh day there was numbness of the left arm, this spread to the left leg and to the left side of the face There were a number of attacks of numbness of this character during the following day, each attack lasting for about 20 minutes There was transient diplopia Her appetite became poor A lumbar puncture was performed, the fluid registered 400 Mm of water There were four cells in the fluid

Examination—Patient is a well developed, large woman She was very drowsy At the time of her admission to the hospital her pulse, temperature, respirations and blood pressure were normal, but there was a slight trace of sugar and albumin in the urine There was bilateral papilledema of four diopters in each eyeground and one large flame shaped hemorrhage just below the left disk The left external rectus was paralyzed

Trephine and Air Injection—January 13, 1936 The right ventricle was tapped, the fluid did not appear to be under increased pressure Fifteen cubic centimeters of fluid were removed and 10 cc of air injected The ventricular system was entirely normal Patient remained in the hospital only five days Her general condition improved rapidly Since the attack of intracranial pressure was so acute, the vision was unimpaired, and since her vision could be carefully watched, a decompression was not considered necessary It was hoped that the condition would clear spontaneously At the time of her discharge there was no apparent difference in the eyegrounds and the abducens palsies remained

Subsequent Course—Letter May 15, 1936 (four months after admission to the hospital) Patient reports that she is perfectly well in every way Her double vision has cleared Ophthalmoscopic examination is entirely negative

Case 22—Unit 74786 A K M Age 21 January 4 to 13, 1937

Complaints—Headache and dimness of vision when reading

Present Illness—Began eight months ago with headaches which were generalized There has been some dimness of vision during the past eight months He has had no other symptoms A lumbar puncture had been performed a week before admission, which registered 250 Mm of water Subsequently, when tested by us, it was 300 Mm

Examination—Patient is a well nourished, normal appearing young man, age 21 Blood pressure 130/75 Blood Wassermann and roentgenologic examination of the head are negative The neurologic examination is entirely negative, except for bilateral papilledema of one and two diopters in each eye There are no hemorrhages in the eyegrounds Vision is 20/30 in the right eye, and 20/40 in the left Visual fields are normal Blind spots are not enlarged

Trephine and Air Injection—January 8, 1937 Only about 5 cc of fluid were obtainable Ten cubic centimeters of air were injected, each ventricle being filled independently The ventricular system was very small, but of normal shape A tumor could be definitely excluded

A lumbar puncture was made three days later in order to check the previous findings of increased pressure It now registered 300 Mm of water, and contained three cells, globulin negative, Wassermann negative A decompression is held in abeyance awaiting visual examination a month hence

Subsequent Course—Patient was well and had normal vision on May 1, 1937 (four months)

Age and Sex Incidence—The youngest patient was nine and one-half, the next 13 years of age, the latter had much the more rapid and severe intracranial pressure in the series One other case was under 20, and a fourth just 20 Seven occurred in the second decade Half of the patients were,

therefore, in the first two decades and the remaining in the third and fourth decades. The oldest patient in the series was 48.

Sixteen of the patients were females and only six were males. Two (females) were colored.

Symptoms—Headache or pain was the first symptom in 17 cases, blurring of vision was the first symptom in four cases, although in two it was practically synchronous with the headache. Dizziness, drowsiness and vomiting were the other three initial symptoms.

Dizziness—a sensation of swooning or uncertainty in the head, not a sensation of whirling objects—was a fairly common disturbance and was doubtless a symptom of intracranial pressure and not of localizing import. It occurred in 12 of the 22 cases.

Nausea was present in seven, vomiting in 11, and diplopia in 11 of the 22 cases. These symptoms occurring in about half of the cases are also due to intracranial pressure.

Duration of Symptoms—In 13 of the 22 cases the symptoms had been present less than a year when the patient applied for treatment. The shortest duration of symptoms was 12 days, another was three weeks, in neither of these were the symptoms severe and in neither was an operation performed. In several cases the symptoms were of only three months' duration. The most fulminating case in the series had had symptoms only ten weeks and was then permanently blind in one eye. Symptoms were present for a year or more (five years in one) in six cases (22 per cent).

The Eyegrounds—In every case papilledema was present and was the outstanding objective finding. In every instance (excepting one patient who had only one eye) the papilledema was bilateral and usually it was symmetrical, occasionally it was slightly greater in one eye. The papilledema varied from one to four diopters. Hemorrhages were very common (15 of the 22 cases). In 11 cases the hemorrhages were bilateral, in four unilateral. Usually they were multiple and scattered over or beyond the disks, in two cases only a single hemorrhage was found in the eyegrounds.

Vision—Blurring of vision was one of the most common complaints. Reduction in visual acuity, enlarged blind spots, scotomata and blindness were found in 11 cases (50 per cent).

Other Symptoms—Numerous other complaints have been assembled but with few exceptions there is no semblance of uniformity. The most common complaint, except those enumerated above, was staggering gait in four cases, though in one instance it lasted for only one day. In six cases there was numbness of some part or parts of the body. There were episodes of numbness in both hands (two cases), a leg, an arm, one side of the face and half of the body (each one case), weakness of both arms and legs (one case) and transient hemiplegia (one case). Buzzing of one or both ears was a symptom in three cases. Other complaints were drowsiness in spells (one), nycturia (one), hallucinations (one), anosmia (one), stiffness of neck (one), pain in lumbar region (one) and loss of weight (one).

SUPPLEMENT

TO THE ARTICLE BY

DOCTOR WALTER E DANDY
BALTIMORE, MD

ON

INTRACRANIAL PRESSURE WITHOUT
BRAIN TUMOR

DIAGNOSIS AND TREATMENT

Findings from Various Examinations—The neurologic examinations were practically negative in every case. A positive Romberg was disclosed only once, hyperactive knee jerks, once, abducens palsy, twice. In only a single instance did the roentgenologic examination disclose a positive finding, the frontoparietal sutures were separated in a girl of 13 who had the extreme intracranial pressure over a short period of time.

The blood pressure was elevated in only one instance, it was 150/90 in a woman age 29. At an earlier examination it was said to have been 170/100. Her urine also contained two plus albumin.

In only one case was the Wassermann reaction positive in the blood and spinal fluid. He gave a definite history of syphilis.

The Cerebrospinal Fluid—With two exceptions the cell count and globulin were well within normal limits. In one case a lymphocyte count of 36 was recorded. A year later on reexamination there were 16 cells. She also had 50 mg. of albumin. She is still living and well six years later, so there can be no serious significance to the increases. In only one other case in the series was there globulin in the cerebrospinal fluid (the patient with syphilis).

Intracranial Pressure—The pressure of the spinal fluid varied from 250 to 550 Mm. of water. In Case 12, a girl, age 13, the frontoparietal sutures were separated by the intracranial pressure. This was evident by percussion of the head (MacEwen's sign) and in the roentgenograms. In no other case in the series was the roentgenologic examination of any value.

Ventriculography—In every instance the ventricles have been small—usually markedly undersized—and symmetrical. An intracranial tumor causing the grade of intracranial pressure that is indicated by the papilledema, hemorrhages and measured pressure could not exist with such small symmetrical ventricles.

Treatment—The treatment of these cases is purely upon a mechanical basis. A right subtemporal decompression is performed if the symptoms and objective signs (eyegrounds and vision) indicate its need. It is necessary in most, but not all, cases because the intracranial pressure frequently persists for months, and frequently years. In four cases in this series there was every indication of a mild degree of intracranial pressure but since the vision and eyegrounds could be periodically observed they were not operated upon. So far, in every case there has been every indication of a complete, spontaneous cure. When operation is indicated the maximum opening in the subtemporal region should be provided. Although the pressure is always high, the cortex has never ruptured in the bony defect. The latter complication is avoided because sufficient fluid escapes from the subarachnoid space to reduce the pressure. Nor has the decompression—although very full and tense—suggested the need of further temporary relief by puncture of the spinal canal. There was one exception to this statement, the little girl previously mentioned with the extreme pressure (Case 12). Following a spinal puncture with collapse of the decompression, the pressure returned to its maximum within an hour.

SUMMARY AND CONCLUSIONS

The facts concerning this condition may be summed up from the 22 cases reported, as follows. There is intracranial pressure of varying duration and intensity. Frequently it persists over several years, though it may be of only a few months' duration. Usually in each individual there are marked variations in the degree of intracranial pressure from time to time and the changes from one extreme to the other and in either direction may occur, at times at least, very rapidly, *i e*, over a period of a few minutes. The subjective disturbances are those of intracranial pressure alone, though at times vague neurologic symptoms may appear, the latter, when present, are fleeting, inconstant, and too ill defined to be of localizing significance. This condition is both immediately and permanently controlled (possibly with rare exceptions) by a subtemporal decompression. To this extent, therefore, it is a self limited disease. Without operative relief, vision, at least, is lost. On the other hand, spontaneous recovery may result before vision is seriously affected. The effect upon life is difficult to estimate, but it is quite probable that in only the most severe grades would life be lost.

The cause of this condition is not known. It can be reasoned with safety that the increased intracranial pressure is dependent upon the intracranial fluid content, *i e*, either blood or cerebrospinal fluid, otherwise the very rapid changes could not occur. But whether blood or cerebrospinal fluid is chiefly or entirely responsible can only be conjectured. Moreover, the variable fluid content must be in the brain itself and not in the meningeal spaces. Proof of this statement is demonstrated by two observations: (1) The protruding brain at the time of operation is usually only partially, and at times scarcely at all, relieved by evacuating the fluid from the subarachnoid spaces over the temporal lobe, and (2) because the ventricular system is always small, and usually much smaller than normal. If the fluid in the meninges were increased the ventricular system would naturally participate and, therefore, be correspondingly enlarged from the backlog. Since fluid is never in the subdural space the only other place where it could form in excess and cause intracranial pressure would be in the substance of the brain. Fluid in this position would maintain the fulness of the brain after evacuating the subarachnoid space and would also diminish rather than increase the size of the lateral ventricle. Whether or not such a condition actually obtains, or could obtain, I do not know. Disturbances of this kind are not known, nor is there sufficient information concerning the circulation of fluid within the brain to advance a hypothesis of this kind.

The only other possible explanation of the increased pressure is by variations in the intracranial vascular bed probably by vasomotor control. It is, I think, more amply demonstrated that such influences are at work. There are at least two reasons for thinking that this may be the most satisfactory explanation. The very rapid increase and decrease of the decompression—in two or three minutes from one extreme to the other—could hardly occur except from variations in the vascular bed, certainly the change is much too

rapid for an increase or decrease of cerebrospinal fluid. And secondly, fright, fatigue, mental or physical, and sudden nervousness may cause the decompression to become more tense very rapidly. However, an abnormal psychogenic background in three patients is certainly the exception rather than the rule. In not more than one, or at most two instances, was the patient highly emotional. On the other hand, these sudden changes may be merely effects that are superimposed upon the underlying condition with another explanation. Nor is there any reason to believe from a study of these patients that the underlying condition can be dependent upon any obstruction in the big venous sinuses, for the Queckenstedt test is usually made routinely and has never been positive. Other etiologic factors are entirely unknown.

That all of these cases have, or have not, the same underlying cause I do not know. We may well be dealing with a condition that has more than one underlying anatomic or etiologic basis. The facts do not permit discussion of this thought. They behave in much the same way, except in degree and duration. Four cases with signs and symptoms of lesser degree were observed without operation and recovered in a few months. One was so fulminating that blindness of one eye resulted in two months, and three months after a seemingly complete recovery, with a collapsed decompression, the pressure again suddenly became extreme and vision was abolished in the remaining eye, within another month the pressure again returned to, and has since remained, normal, with partial return of vision in this eye. Despite every search no cause of the original or subsequent increased pressure could be suggested. She was a very placid girl and only 13 years old (Case 12).

One patient feels that "after reading or talking to people the decompression may get as tight as a drum, and within two minutes it may be perfectly soft." He also thinks that nervousness (he is not of nervous temperament), or getting in or out of a car, will cause a sudden increase in the pressure. He also thinks the decompression is more tense when he is constipated. Another patient who is chronically constipated does not think there is any relationship between the degree of pressure and her constipation, nor is there any appreciable difference.

In only one case is there reason to consider an inflammatory lesion, such as an encephalitic process, as a possible factor in this condition. In Case 5 the cell count (36) and globulin were increased, and a year later the cell count was still 16. It may well be that this case differs from the others, although the end-result is essentially the same. Certainly there have been numerous neurologic complaints in this case, although no objective findings. Indeed the history in the case is not unlike that of multiple sclerosis, but after five years she is again without neurologic symptoms. It is worthy of note also that this patient went a year with her intermittent pressure and without diminution of vision. On the whole, the periods of increased pressure may well have been of short duration.

Nor can it be denied that syphilis is a factor in Case 16, in which the Wassermann reaction from both blood and cerebrospinal fluid was positive.

In none of the remaining cases, however, do the examinations of the spinal fluid suggest an underlying inflammatory lesion of any type

That the increased pressure usually sets its limit within the bounds of relief afforded by a subtemporal decompression is indeed surprising. In one case this was certainly not true, for the vision was lost when the decompression became more tense than any I have ever seen, recovery of vision followed the spontaneous relief of the underlying condition. It is quite certain that vision and probably even life itself were spared by the decompression that had been made.

The significance of papilledema in these and other cases of suspected intracranial pressure should be emphasized. Needless to say there is no difference between the ophthalmoscopic picture in these cases and those due to tumors, for both are due to intracranial pressure. There is another ophthalmoscopic picture, however, where a differential diagnosis is all important, *i e*, optic neuritis. Although it is, at times, possible by the ophthalmoscopic studies to differentiate between a mechanical papilledema due to pressure and the local one of optic neuritis, this is usually not true. In fact in a condition so serious, I should rarely feel safe in depending exclusively upon an ophthalmoscopic examination for the differentiation of these two lesions. But the differential diagnosis can be, and always should be, made by directly ascertaining the intracranial pressure.

The diagnosis of this condition is made by the ventriculograms and by measurement of the pressure of the cerebrospinal fluid. It may be reasoned that a tumor is really present and has been overlooked. If ventriculograms are properly made and carefully interpreted, no single brain tumor can fail to escape diagnosis and localization. It is possible for multiple metastatic tumors to exist throughout the brain and not appreciably deform the ventricular system. Moreover, most of the cases in this group have stood the test of time. It is not conceivable that tumors would be disclosed after several years.

Visualization of the lateral cerebral ventricles should be made by injecting air into them directly (not by lumbar puncture). If the ventricular system is normal a tumor can be excluded with absolute certainty. If there then remains any doubt whether the intracranial pressure is increased, a lumbar puncture can then be safely performed and the pressure measured. To inject air in the presence, or suspected presence, of intracranial pressure is far too dangerous to be justifiable. The secondary spinal puncture for pressure readings can be made immediately or a few days later—I usually prefer the latter though the severity of the symptoms may dictate its prompt performance. When the lateral cerebral ventricles are small the indications of increased intracranial pressure from the ventricular puncture may be absent or equivocal, it is for this reason that so many of these cases have had the spinal in addition to the ventricular puncture. Given increased pressure plus papilledema the diagnosis and indications for mechanical treatment are clear.

Without increased pressure it is equally evident that the ophthalmoscopic picture is one of optic neuritis and operative treatment is contraindicated

The periodic nature of the attacks, and also the permanency of cure in four cases known to have remained well without treatment, lead one to suspect that this condition may be a very common one and that only the most severe grades fall into our hands, and that many of the transient, unexplainable headaches may really be instances of this condition, though in lesser degree

DISCUSSION —DR WILDER G PENFIELD (Montreal) I should like to ask Doctor Dandy if he feels that there may not be an increase in subdural fluid in those cases. Occasionally it does happen secondary to an inflammatory process in the mastoid or one of the sinuses, or secondary to trauma, that there is definite increase of subdural fluid. The subdural fluid has a higher protein content which is unable to pass through into the subarachnoid space because of the presence of that protein. Such fluid escapes at decompression and the pressure is relieved. It is difficult to be sure, in any surgical approach, where fluid comes from.

DR ALFRED ADSON (Rochester, Minn.) There is no question but that this group does exist. In addition, I think probably we also have had the experience of examining patients who have come with the symptoms of intracranial pressure and even localizing evidence, and have used ventriculography in connection with exploration, at which time no tumor was found. A biopsy made in conjunction with exploration resulted in the report of inflammatory tissue, and I have had the same patients return several years later seeking medical release in order that they might be accepted for life insurance. It is very evident that these patients did not have brain tumors and that some of these undoubtedly had localized encephalitis. We have encountered a number of cases of retrobulbar neuritis in which there were choked disk and evidence of intracranial pressure. It was our impression that probably we were dealing with some type of leptomeningitis.

DR WALTER E DANDY (Baltimore) closing. I can answer Doctor Penfield's suggestion very positively. When a temporal lobe is exposed, one can, of course, see where the fluid is coming from, and it is always from the subarachnoid space. You can clearly see it coming through the arachnoid membrane.

I do not think Doctor Adson's suggestion of encephalitis probably belongs in this group. Certainly the effects of an encephalitis would not exist over as long a period as five, six or seven years. I think that is a different lesion. But neither would it account for the very sudden fluctuations in the size of the decompression for which the only explanation I can offer is that it probably has some relationship to the intracranial vascular bed. How could a decompression rise in two or three minutes and then fall in the same length of time, except from a sudden change in the vascular bed? There could scarcely be a rise and fall in the amount of cerebrospinal fluid so rapidly.

THE PLACE OF EXPLORATORY OPERATION IN THE SURGERY OF SUBPHRENIC ABSCESS

A REPORT OF NINE NEGATIVE EXPLORATIONS

EDWIN P. LEHMAN, M.D.

UNIVERSITY, VA.

FROM THE DEPARTMENT OF SURGERY AND GYNECOLOGY, UNIVERSITY OF VIRGINIA SCHOOL OF MEDICINE, UNIVERSITY, VA.

THE difficulty of diagnosis of subphrenic abscess is emphasized by all who have written on the subject. Reports in the literature, however, cover almost without exception only those cases in which diagnoses were correct. Inasmuch as no one has heretofore reported his failures as well as his successes, there is no way of estimating how difficult the diagnosis of subphrenic abscess actually is. It is apparent that only such complete presentation can furnish a comprehensive view of the diagnostic problem. The present study presents nine cases of operative exploration of the subphrenic space for abscess in which no infection was found, and compares them with 20 cases of proven subphrenic abscess. It approaches the subject, therefore, from a new direction, being in part rather a study of the diagnosis of subphrenic abscess than a study of the disease itself.

Operative exploration of the subphrenic space has been suggested by several authors as a means of diagnosis to replace exploration by aspiration. As these authors have had reason to suggest the employment of exploratory operation, they must also have had difficulties in diagnosis. Furthermore, it seems a logical probability that they must have explored at times without finding abscess. And yet, in this regard also, the literature is almost silent. In addition to the comparison of proven cases with cases mimicking the clinical picture of subphrenic abscess, the present study will consider the propriety of exploratory operation in the diagnosis of this condition on the basis of the nine negative explorations.

The 20 cases of proven subphrenic abscess (here compared with the nine cases in which exploration revealed no abscess) have recently been presented from the usual point of view by Lehman and Archer⁶. The review of the total series of 29 cases reveals a surprisingly imperfect attainment of diagnostic accuracy (Table I). Of the 20 cases of proven abscess, three cases were not operated upon, the diagnosis having been missed. In two others, operation was performed under mistaken diagnosis. These five cases, together with the nine negative explorations, yield 14 incorrect diagnoses as compared with 15 correct diagnoses (51.7 per cent correct)*.

* In addition there were studied 19 cases in which the diagnosis of subphrenic abscess was considered or made, but in which the final diagnosis is unknown. This group is not included here for obvious reasons. Were the correctness of diagnosis in this group known, the above percentage might be altered in either direction.

SUBPHRENIC ABSCESS

TABLE I

MATERIAL AND ACCURACY OF DIAGNOSIS

Group I—Subphrenic Abscess*	
(1) Operation	
(a) Correct diagnosis	15
(b) Incorrect diagnosis	2
	—
Total	17
(2) No operation	
(a) Diagnosis at autopsy	2
(b) Diagnosis in chronic stage	1
	—
Total	3
	—
Grand total	20
Group II—Negative Explorations	9

SUMMARY

(1) Correct diagnoses	15
(2) Incorrect diagnoses	
(a) Missed when present	5
(b) Operation when not present	9
	—
Total	14

* This diagnosis is limited to abscess in the three suprahepatic spaces and includes no infrahepatic abscess (Cf reference 6)

In contrast, however, the hospital mortality rate for 17 cases of proven subphrenic abscess operated upon is more satisfactory than is the diagnostic record. This rate, 23.5 per cent, is about three-quarters of the average post-operative hospital mortality as calculated by Ochsner and Graves⁹ from summation of an extensive literature, and less than the corresponding mortality in 22 of 27 individual reports tabulated by them. The possible significance of the combination of poor diagnostic results with a satisfactory record of surgical treatment will receive comment later.

Neither the correct diagnoses nor the errors of diagnosis in the cases herein studied mirror the diagnostic acumen of a single surgeon. Seven visiting surgeons are responsible for decision as to treatment of the cases, although a few of the operations were actually performed by resident surgeons (Table II). An analysis of the distribution of errors indicates that the surgeons with the greatest opportunities for diagnosis have made the highest proportion of errors and that the proportion of errors is, among these men, surprisingly equal.

The diagnosis of subphrenic abscess depends upon three main factors: (1) Demonstration of a preexisting disease commonly associated with the onset of subphrenic infection, (2) physical findings, and, (3) roentgenologic manifestations. A comparison of these factors in the cases proven to have subphrenic abscess with those in the cases proven not to have this condition

will next be attempted. A fourth factor frequently emphasized, namely, the course of the disease, is admittedly extremely variable⁹ and does not lend itself to analysis.

TABLE II
DISTRIBUTION OF ERRONEOUS AND CORRECT DIAGNOSES
AMONG SURGEONS RESPONSIBLE

Surgeon	Abscess Present, Other Diagnosis Made (From Group I)	Abscess Present, Diagnosis Not Made (From Group I)	Negative Explorations (Group II)	Total Wrong Diagnoses	Correct Diagnoses (From Group I)
A	0	2	6	8	7
B	0	0	2	2	2
C	1	1	1	3	2
D	0	0	0	0	2
E	0	0	0	0	1
F	0	0	0	0	1
G	1	0	0	1	0
Totals	2	3	9	14	15

In Table III are compared the known etiologic factors in 20 proven cases of subphrenic abscess (Group I) and the supposed etiologic factor in cases wrongly treated as subphrenic abscess (Group II). Many of the same common etiologic conditions are present in each group, and the proportional distributions are roughly similar.

TABLE III
PRECEDING DISEASE REGARDED AS ETIOLOGIC
(Groups I and II)

Disease	Group I	Group II
(1) Peritonitis from		
(a) Appendicitis	9	3
(b) Salpingitis	0	2
(c) Septic abortion	1	0
(d) Empyema of gallbladder (?)	0	1
(e) Acute pancreatitis	1	0
(2) Perforation of		
(a) Duodenum, ulcer	2	1
(b) Bowel, gun shot	1	0
(c) Cecum, carcinoma	1	0
(d) Liver, gun shot	0	1
(3) Operation on		
(a) Biliary tract	3	1
(b) Pylorus	1	0
(4) Unknown	1	0
Totals	20	9

SUBPHRENIC ABSCESS

In comparing the clinical data in the two groups (Table IV), uneven thoroughness of notes has made two assumptions necessary. In items one to four inclusive, if neither positive nor negative statements are recorded, the case is entered in the column "Not noted." In items six to nine inclusive, if there is a record of examination of the thorax, it has been assumed that all unmentioned findings are absent, whether or not a negative statement is made. In two cases, no record of thoracic examination is available.

TABLE IV
COMPARISON OF CLINICAL DATA
(Groups I and II)

	Signs	Group I			Group II		
		Present	Absent	Not Noted	Present	Absent	Not Noted
1	Elevation diaphragm	10	5	5	5	2	2
2	Fixation diaphragm	2	7	11	2	1	6
3	Tenderness Subphrenic area	4	1	15	3	1	5
4	Tenderness and spasm, abdomen	12	0	8	3	0	6
5	Dullness over Thorax*	5			3		
6	Abnormal breath sounds	7	11	2	6	3	0
7	Râles	4	14	2	3	6	0
8	Pleural rub	1	17	2	0	9	0
9	Altered voice sounds	3	15	2	0	9	0
Average highest W B C †		16,800			17,200		
Average highest fever†		102 8° F			102 8° F		

* Not clinically interpreted as elevation of the diaphragm

† Highest in the period just before operation

In the interpretation of Table IV, one must bear in mind that in 25 out of the entire 29 cases the diagnosis of subphrenic abscess was considered, and that, therefore, failure to note the presence of the classical signs in most instances probably signifies their absence. The figures presented cannot, of course, be of statistical significance. It is intended only to present the general diagnostic patterns in the two groups, the similarity of which is at once obvious. In view of Ochsner's^{9, 14} emphasis on tenderness over the subphrenic area as the most important sign of subphrenic infection, it is interesting that three cases in Group II revealed this finding. None of the three suffered from abscess of the liver. Although the proportion of cases in which no notation was made on this point is too high to permit conclusions, yet it is further suggestive that, whereas in one-third of the cases proven to have no subphrenic abscess this sign was present, it was recorded in only one-fifth of the cases of proven abscess.

In the comparison of roentgenologic diagnosis in the two groups (Table V), it must be remembered that the commonly accepted usefulness of the roentgen ray in the diagnosis of subphrenic abscess depends, in large part, on the thoroughness with which examination can be made. The roentgenologist is

frequently so handicapped by the illness of the patient, that fluoroscopy is impossible, or that only bedside examination is permitted. Furthermore, in some instances, roentgenologic examination may precede operation by several days. No attempt has been made to separate the cases studied inadequately by the roentgen ray, from those that were able to undergo complete examination, inasmuch as the factors leading to inadequate examination operated about as frequently in the cases of subphrenic abscess as in those without subphrenic abscess. When we compare the two groups, the similarity of the patterns presented is again striking. Without assumption of statistical significance, it may be pointed out that subphrenic abscess was suggested roentgenologically in 89 per cent of the cases in which it was absent, and in 76 per cent of the cases in which it was present.

TABLE V
COMPARISON OF ROENTGENOLOGIC DIAGNOSIS
(Groups I and II)

	Group I	Group II
Positive Diagnosis	8	3
"Suggestive" or "Consistent with"	2	4
Alternative diagnoses (one subphrenic abscess)	3	1
Subphrenic abscess not suggested	4	0
No conclusion	0	1
No roentgen ray	3	0
Totals	20	9

The data so far presented have served only to bring to a focus the admitted difficulties of diagnosis of subphrenic abscess by comparing the diagnostic elements in a group of cases of proven abscess with those in a group in which the absence of subphrenic infection was demonstrated. Certain individual cases, familiar to every surgeon, only sharpen the focus. The actual final diagnoses in the group under consideration reveal that fluid in the chest and abscess of the liver most often mimicked the signs of subphrenic abscess (Table VI). The differential diagnosis between abscess high in the liver and subphrenic abscess has appeared impossible to more than one observer.^{3, 12} Of the two cases in which the final diagnosis was undetermined, one died of continued sepsis and no autopsy was permitted. The other is classified here only for want of a better category. This patient appears also in Group I. He was operated upon by the anterior transperitoneal route and an anterior subphrenic abscess was drained. He continued to have fever up to 103.5° F, and it was feared that a posterior, undrained abscess was also present. A posterior extraperitoneal exploration^{8, 12} 12 days after the anterior operation, revealed the posterior portion of the right subphrenic space to be free from acute disease. The cause of his fever which continued for 19 days longer was never determined, and he ultimately recovered.

SUBPHRENIC ABSCESS

TABLE VI

FINAL DIAGNOSES IN CASES PROVEN NOT TO HAVE
SUBPHRENIC ABSCESS

(Group II)

I	Fluid in chest	
1	Simple effusion	1
2	Empyema	
	(a) Simple	2
	(b) Interlobar	<u>1</u>
		4
II	Liver abscess	3
III	Undetermined*	<u>2</u>
		5
	Total	9

* See text

The dilemma presented by the difficulties of diagnosis of subphrenic abscess has been met in past years by diagnostic aspiration. Although most surgeons condemn this procedure for either its uselessness¹⁰ or its danger, or both, the need for some positive means of diagnosis is so great that compromises in its use are often suggested. The commonest of these compromises is the proviso that aspiration be undertaken only if operation immediately follows^{1, 4, 5, 13}. If aspiration may cause contamination of a clean pleura, which is the danger feared, then it is hard to see how operation, immediate or not, can prevent such contamination. Another compromise suggested for the same purpose is aspiration by an extraserous route^{2, 9}. No one has reported on the results of this method. If it is difficult to find a subphrenic abscess with a needle introduced directly through the chest, it would seem a matter of remote chance if any but the largest abscess could be encountered by a needle pushed upward from below the twelfth rib. In a word, it is probably sound doctrine to discard without compromise aspiration for diagnosis of subphrenic abscess.

In these confusing cases, then, there remains only exploratory operation. But exploratory operation cannot be accepted as a proper means of diagnosis unless it can be shown not to entail a prohibitive risk. There is nothing in the literature that throws any light on risk in the type of case which may simulate subphrenic abscess. Russell,¹¹ Schwartz,¹² Doherty and Rowlands,² Ochsner and Graves,⁹ Janz,⁵ and Overholt and Donchess¹⁰ all suggest the propriety of the procedure. None except Doherty and Rowlands² report failure to find abscess at operation, and their report is limited to the statement that they have three times operated with negative findings. Analysis of the mortality in nine negative explorations should offer evidence as to the propriety of diagnostic operation.

The crude hospital mortality of this group is 55.5 per cent (Table VII), a figure which at first glance would tend to discredit exploration. However, the apparent causes of the deaths of these patients, proven at operation

in one case and at autopsy in two cases, are conditions which in themselves carry a high mortality. Moreover, the interval between exploration and death in four out of five cases, 10, 11, 17, 51 and 18 days respectively—suggests that in each instance the patient died of the disease for which operation was wrongly undertaken and that the operation could have had little to do in determining the fact of death, although it might have hastened to an indeterminate degree the time of death. In the remaining case, the interval between exploration and death was only three days. Here we cannot absolve the operation from apparent blame, even though in this instance it demonstrated that the patient was suffering from a disease almost certainly fatal in itself. It must be remembered that all these patients were extremely ill, suffering from multiple pathologic conditions (Tables III and VI), and that the operations were regarded in several instances as desperate remedies. Although figures of the present magnitude are of no final significance, they suggest that exploration of the subphrenic space has had surprisingly little apparent effect on the death rate.

TABLE VII

CAUSE OF DEATH AND INTERVAL BETWEEN OPERATION AND DEATH
IN CASES EXPLORED WITHOUT FINDING ABSCESS

(Group II)

I Mortality	
Total negative explorations	9
Total hospital deaths	5
Mortality	55.5%
II Cause of Death	Interval between exploration and death, and method of final diagnosis

Cause of Death	Days between Exploration and Death	Final Diagnosis by
Liver abscess, multiple	3	Operation
Liver abscess, multiple	11	Autopsy
Pneumonia and empyema	17	Autopsy
Pulmonary embolus	51	Clinical
Undetermined (continued sepsis)	18	

No attempt is made to correlate the types of operation employed in this series with the mortality, as the methods are too diverse among so few cases. As experience has grown both with operation for actual subphrenic abscess and with exploration for supposed subphrenic abscess, opinion has become crystallized that the principles enunciated by Nather and Ochsner⁸ are sound—namely, the employment of local anesthesia and the extraserous approach. It is believed that only adherence to these principles will justify exploratory operation under any circumstances.

COMMENT—In a general discussion of the place of exploration in the diagnosis of subphrenic abscess, the cases in which exploration will be undertaken may be profitably divided into three categories. (1) Those in which

subphrenic abscess is actually uncovered, (2) those in which the symptoms and signs are due to liver abscess, and (3) those in which they are due to infection above the diaphragm. In the first category, of course, exploration becomes therapy. In the second category, a properly placed exploration may also permit therapy. In a recent case of gunshot wound through the liver, included in Group II of this series, in which symptoms, signs, and roentgenologic findings were entirely characteristic of subphrenic abscess, exploration of the subphrenic space, which showed no infection, permitted drainage of a large solitary abscess of the liver with ultimate recovery of the patient. Only the third category, then, offers an important possibility of doing harm rather than good by exploratory operation.

In the earlier experience covered by this report both radiologist and surgeon were disturbed by the failure to find an abscess when abscess had been diagnosed. Confidence in diagnosis evaporated, and the present study resulted. From it the conclusion has been reached that a salutary lack of confidence in diagnosis must remain as the normal approach to these difficult paraphrenic problems. Regret is experienced if exploration is negative, but such an outcome is no longer shocking. The recognition of exploratory operation as a relatively safe court of final diagnostic appeal has furnished a sense of assurance in the approach to problems of infection in the region of the diaphragm that neither clinical methods nor roentgenologic evidence can furnish. It should be emphasized that exploration is justified only as a court of final appeal, but it should further be emphasized that appeal to that court need not be too long delayed.¹⁰

It is generally agreed that one great cause of failure to diagnose subphrenic abscess is failure to think of it as a possibility. In four of the five cases of proven subphrenic abscess in which diagnosis was not made, the possibility was not considered. If one is on the alert for subphrenic abscess, earlier operative treatment on the average should result, and mortality should thereby be lowered. By the same token, a greater number of negative explorations should be performed. It is too much to assume from the figures presented herein that the low operative mortality in proven abscess (23.5 per cent), and the relatively large number of negative explorations, bear any relationship to each other. It is suggested, however, that larger statistics might well demonstrate such a relationship.

Finally, it may be repeated that there is no way accurately to compare the present unquestionably poor diagnostic record with experience at other clinics. Every commentator emphasizes the difficulty of diagnosis, but no commentator has heretofore attempted to measure the difficulty by reporting errors as well as successes. The question is presented in the hope that this confession may lead to further studies of the same nature. It is further hoped that the percentage of correct diagnosis in other hands may prove to be greater than the slightly better than 50 per cent reported here (Table I). Even if it is considerably greater, there will certainly remain cases in which exploration must be undertaken in the absence of positive diag-

nosis, and there will probably remain cases in which a positive diagnosis is proved by operation to be fallacious. In conclusion, it is hoped that the place of exploratory operation under such circumstances may receive more adequate discussion than has heretofore been accorded to it.

REFERENCES

- ¹ Bogart, L. M. Subphrenic (Subdiaphragmatic) Abscess. *Am Jour Surg*, 26, 467, 1934.
- ² Doherty, W. D., and Rowlands, R. P. Subphrenic Abscess. *Brit Med Jour*, 1, 168, 1931.
- ³ Elsberg, C. A. Contribution to the Pathology, Diagnosis, and Treatment of Subphrenic Abscesses after Appendicitis. *ANNALS OF SURGERY*, 34, 729, 1901.
- ⁴ Gatewood. Subphrenic Abscess. *Am Jour Med Sci*, 180, 398, 1930.
- ⁵ Janz, G. Über subphrenische Abszesse. *Arch f klin Chir*, 178, 482, 1934.
- ⁶ Lehman, E. P., and Archer, V. W. Suprahepatic (Subphrenic) Abscess. *Southern Surgeon*. In press.
- ⁷ LeWald, L. T. Subphrenic Abscess and Its Differential Diagnosis Roentgenologically Considered. *Arch Surg*, 10, 544, 1925.
- ⁸ Nather, C., and Ochsner, A. Retroperitoneal Operation for Subphrenic Abscess. *Surg, Gynec, and Obstet*, 37, 665, 1923.
- ⁹ Ochsner, A., and Graves, A. M. Subphrenic Abscess. Analysis of 3372 Collected and Personal Cases. *ANNALS OF SURGERY*, 98, 961, 1933.
- ¹⁰ Overholt, R. H., and Donchess, J. C. Subphrenic Abscess. *New England Jour Med*, 213, 294, 1935.
- ¹¹ Russell, T. H. Subphrenic Abscess. *ANNALS OF SURGERY*, 90, 238, 1929.
- ¹² Schwartz, J. Suppuration in the Subphrenic Region. *Arch Surg*, 20, 317, 1930.
- ¹³ V. Szacsavay, I. Zur Klinik der subphrenischen Abszesse. *Beit z klin Chir*, 160, 591, 1934.
- ¹⁴ Personal communication.

DISCUSSION—DR HOWARD LILIENTHAL (New York) I feel that subphrenic abscess comes under the head of thoracic surgery, as well as abdominal surgery. I should like to say a word about the matter of diagnosis, particularly in relation to the induction of pneumoperitoneum, followed by a roentgenologic examination in the upright position. You will find that there will be an era of transparency above the liver and below the diaphragm, which you can make out if there is no abscess. If there is an abscess this transparent area will be absent and, also, if the patient has pleurisy, which is common enough, suppurative or not, on account of the presence of the subphrenic abscess, you will be able to establish the probable diagnosis. On the contrary, if there is a sacculated low empyema or a supraphrenic empyema, then the air bubble will be an almost positive proof that no subphrenic abscess is present.

I feel very strongly concerning the technic of operation. You have heard what both Doctor Lehman and Doctor Ochsner have said against a transverse approach. As a thoracic surgeon, I believe that the simplest and perhaps the safest method is a transthoracic approach by the following method. The patient is prone with a bulky pillow under his belly, so that his pelvis is high and his head down. This tends to force the lower pleural layers together. It is known as Elsberg's position. One then makes a resection, say, of the ninth or tenth rib—I usually resect the ninth rib—a fairly long piece under local anesthesia, and enter the pleura deliberately, without any danger of invading the subphrenic space. The external layer

of the pleura is then sutured to the internal layer of the pleura—not the *visceral* pleura. After that has been done, and a piece of gauze laid over the suture line, the pleura-covered diaphragm is very clearly seen, and one is perfectly safe in undertaking aspiration. You will not only ascertain whether or not there is a subphrenic abscess, but whether or not there may be a liver abscess with or without subphrenic pus. If one does not find anything by aspiration, he may be quite sure pus is present, personally I have no hesitation in incising the diaphragm. It is a simple enough thing in these circumstances to suture this incision if desired, and I believe that I have saved patients who probably would not have been saved had the exploratory operation proved negative in spite of the presence of abscess.

DR EDWIN BEER (New York) As a diagnostic aid in obscure cases of suspected subphrenic abscess, it seems to me we have all forgotten Carelli's work on perirenal insufflation. We are studying the possibility of recognizing these subdiaphragmatic closures by exudate and abscess by this method, having found that these perirenal insufflations with air, carbon dioxide, or oxygen outline not only the kidneys and the adrenal gland in most cases, but fill out the spaces directly under the diaphragm. I would, therefore, recommend this procedure for diagnostic trial. I think we are going to have some very satisfactory results to report.

DR ALTON OCHSNER (New Orleans) It is indeed gratifying to learn that exploratory operations are being used for subphrenic infections. Several years ago, in studying this problem, I reviewed the literature and found that the average length of time following the initial infection was approximately four months. It varied from a few weeks to over 14 months.

It is only by the exploration of the subphrenic space that one can drain a subphrenic abscess early enough. I think it is important to stress that in the subphrenic space, as elsewhere in the body, infections occur which subside spontaneously. We very frequently make a diagnosis of subphrenic infection in which we feel that the infection has subsided spontaneously under conservative therapy, and it is only after observation of these patients for a period of a few days or possibly a week or more that we feel justified in exploring the subphrenic space.

Doctor Lehman has referred to the diagnostic sign of persisting tenderness. In cases of subphrenic space infection following appendicitis we have found the persistence of tenderness over the right twelfth rib to be the most important diagnostic sign. This is usually elicited only on deep, firm pressure, and not by superficial pressure.

I want to subscribe also to the lack of danger of exploration, if the exploration is done extraseptally. In our own clinic we have explored five of these patients and have not found abscesses. Two of them have subsequently died, both from liver abscesses, which were not recognized. The others have gotten well spontaneously of an undetermined infection.

DR EDWIN P. LEHMAN (University, Va.) closing. Doctor Ochsner and I have had a good many arguments about the diagnostic importance of tenderness over the subphrenic space, particularly over the twelfth rib behind. Our experience has been that this finding is not as useful as he feels that it is. It seems to me that, if tenderness is absent in a number of cases in which proven abscess is present, and present in a number of cases in which there has been no abscess, as shown in the material presented, it is difficult to base a diagnosis of subphrenic infection upon this sign.

An interesting case in point was that of a boy who had a spreading peritonitis from appendicitis who was treated conservatively, and localization followed. The abscess was drained, and his temperature came down to normal. Two or three days later it began to rise. The first thing thought of was subphrenic abscess, and for six days the entire staff searched for tenderness over the subphrenic space. On the seventh day tenderness appeared, and a well-established abscess was drained, which had unquestionably been present for nearly a week. It is, therefore, not wise to depend too completely upon this sign.

In regard to the use of pneumoperitoneum in diagnosis as mentioned by Doctor Lilienthal, practically all the cases reported were acute cases with intra-abdominal infection still active, and we have not used it for that reason. Peritonitis will probably prevent its use in the type of case favorable for treatment, that is the early case.

I have had no experience with Doctor Beer's suggestion.

THE CONTROL OF THE HEART BEAT BY THE SURGEON¹

WITH SPECIAL REFERENCE TO VENTRICULAR FIBRILLATION OCCURRING
DURING OPERATION

CLAUDE S. BECK, M.D., AND FREDERICK R. MAUTZ, M.D.

CLEVELAND, OHIO

FROM THE LABORATORY OF SURGICAL RESEARCH, WESTERN RESERVE UNIVERSITY SCHOOL OF MEDICINE AND THE
UNIVERSITY HOSPITALS, CLEVELAND, OHIO

WE ARE recording observations such as one might make during an operation upon the heart. They are of some practical value in the surgery of that organ.

The Effect of Exposure of the Heart—When the heart is exposed at operation, the pressure upon the organ is changed from the subatmospheric pressure that normally exists in the mediastinum to the pressure of atmosphere. With normal respiratory movements this pressure fluctuates between minus 4 and minus 8 cm. of water. When the heart is exposed, this oscillating negative pressure is increased to an almost constant atmospheric pressure. A definite compression effect is produced by this increment of pressure from the atmosphere and is manifested by a corresponding rise in venous pressure, a slight transient fall in arterial pressure, and, in some experiments, a measurable reduction in cardiac output.¹ The normal heart can tolerate these alterations without difficulty. The question arises as to whether a failing heart can tolerate this compression as readily as a normal heart. We believe that a failing heart may not be able to do so. We know of two instances in which death occurred after the mediastinum was opened, and it is probable that atmospheric compression was the "final straw" that stopped the heart.

What is the effect of exposing to the atmosphere a heart that is already compressed as by a scar or by fluid in the pericardial cavity? Naturally, the total compression becomes the sum of the two factors. For example, let us consider a heart that is compressed by a scar to the extent of 40 cm. of water. When the mediastinum is opened at operation, the compression rises to a mean pressure of about 40 plus 6 cm. The compression has moved up closer to the fatal limit. This increment of compression must be tolerated until the scar is removed. Fortunately, this part of the operation is usually of brief duration.

It is interesting to note the effect of air pressure in our patients who were operated upon. Our anesthetist, Mrs. Gertrude Fife, has attempted to determine alterations in blood pressure at the moment the mediastinum was opened. Fourteen patients with coronary sclerosis who were operated upon for the purpose of establishing a new blood supply to the myocardium were analyzed. Seven of these showed a fall of 10 to 35 Mm. of mercury in systolic pressure, three showed a fall of 4 to 10 Mm. and four showed no change. Seventeen

* Aided by a grant from the Josiah Macy, Jr., Foundation.

patients who were operated upon for compression scars were analyzed in this respect. Fourteen of these patients showed a fall in systolic pressure ranging from 10 to 60 Mm of mercury and a fall in diastolic pressure varying from 5 to 40 Mm of mercury. Three patients showed no demonstrable alteration in pressure. The average fall in the compression group was 33 Mm in the systolic pressure and 13 Mm in the diastolic pressure. In the compression group the blood pressure returned to its former level in two to ten minutes. On the basis of these observations, it is interesting to note that the effect of atmospheric compression is more pronounced in the patients who are suffering from chronic compression than it is in the patients without compression of the heart.

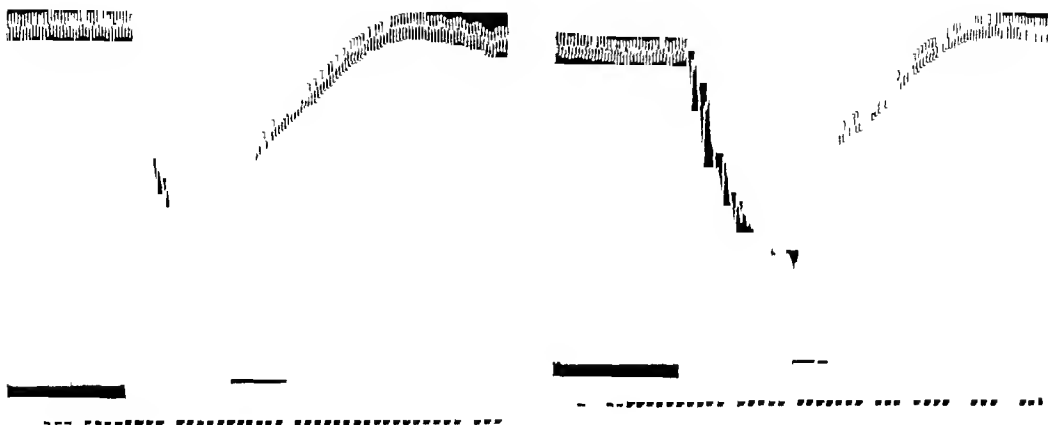


CHART 1—The effect upon arterial tension produced by local pressure applied to the right ventricle. Signal magnet indicates local pressure time in seconds.

CHART 2—The effect upon arterial pressure produced by torsion of the heart. Signal magnet indicates torsion time in seconds. Note the sharp initial recovery followed by a delayed recovery in pressure.

Manipulation of the Heart—The various manipulations to which the heart is subjected at operation can be classified under local pressure, angulation from its normal axis and torsion on its long axis. These displacements are produced in the dissection of scars from the heart, in the suture of cardiac wounds and in our operation of placing grafts upon the myocardium.

Local pressure may be regarded as a form of local compression. It may be produced by a finger, spatula or retractor on the heart. The walls of the two auricles readily yield to pressure from without because the pressure in the auricles is low. The right ventricular wall also is readily inverted. The capacity of each of these three chambers is easily reduced by pressure from the outside. The effect is shown by a rise in the venous pressure and a fall in the arterial pressure (Chart 1). As would be expected, the left ventricle resists local pressure much better than the other chambers do. Local pressure is also deleterious when it is applied over a coronary artery and can produce

extrasystoles, tachycardia or ventricular fibrillation. We observed these reactions in experimental animals and in patients.

Angulation of the heart is possible in three directions. The heart is not angulated posteriorly at operation, although the entire heart seems to fall somewhat posteriorly when the mediastinum is opened at operation. Angulation to the left or right or lifting the heart from its bed produces a rise in venous pressure and a fall in arterial pressure. These dislocations are encountered in the dissection of scars from the heart. Dislocation to the left by retraction on the right ventricle produces great drops in arterial pressure and it is especially harmful. These angulations produce their deleterious effects by interference with blood flow through the great veins at the base of the heart. Similarly, torsion of the heart, either clockwise or counterclockwise, interferes with the blood flow through the great veins. Torsion is encountered in the dissection of scars. We have produced it most commonly in traction upon the scars adherent to the right lateral aspect of the heart. With a left parasternal approach, exposure of the right lateral surface is rendered difficult because of the sternum. We rotate the heart somewhat to get this exposure. This manipulation is deleterious and must not be prolonged (Chart 2).

It is of interest to note that a pull upon the apex in the long axis of the heart is not deleterious to the circulation (Chart 3).

These deleterious responses by the heart produced by surgical manipulations should be heeded by the surgeon. If they are disregarded, the arterial pressure vanishes and the heart rate becomes irregular and rapid. Auricular fibrillation and finally ventricular fibrillation develop. These serious complications can be avoided by giving the heart frequent rest periods. In these periods of rest the operation is stopped and the operative field is protected by a moist pack. The response of the heart to periods of rest is shown in Chart 4. In our operating room organization these rest periods are determined by our cardiologist, Dr. Harold Feil. We believe that rest periods are of very great importance for success in cardiac operations.

Surface Stimulation—The heart may receive many abnormal stimuli during the course of an operation. These mechanical stimuli coming from the surface of the heart are not effective during systole, which is the refractory period of the heart beat, but many of them are effective during diastole. Each extrasystole is followed by a compensatory pause. One extrasystole with its compensatory pause produces a momentary drop in arterial pressure. It

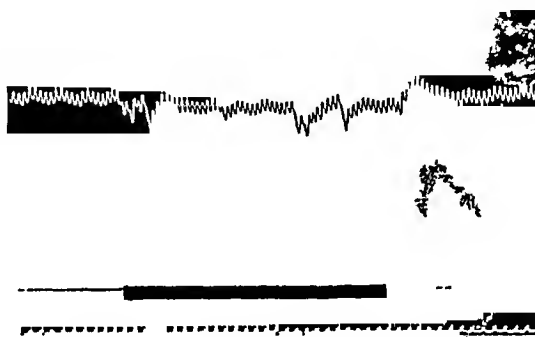


CHART 3—The effect upon arterial pressure produced by a strong traction applied to the apex and exerted in the long axis of the heart. Signal magnet indicates traction time in seconds. No significant change is produced. The result obtained in this acute experiment is in agreement with the results of recovery experiments. Dilation, hypertrophy and failure of the heart do not occur after the heart has been attached to the diaphragm.

has been our experience that these stimuli sent in over a period of minutes seriously affect the heart. Irregularities, tachycardia and low arterial pressure result.

Experimentally, ventricular fibrillation and auricular fibrillation have been produced by showers of stimuli sent in by surface dissection. These same reactions have been seen at operations on the human heart, and the surgeon and assistants should be on the alert to note them.

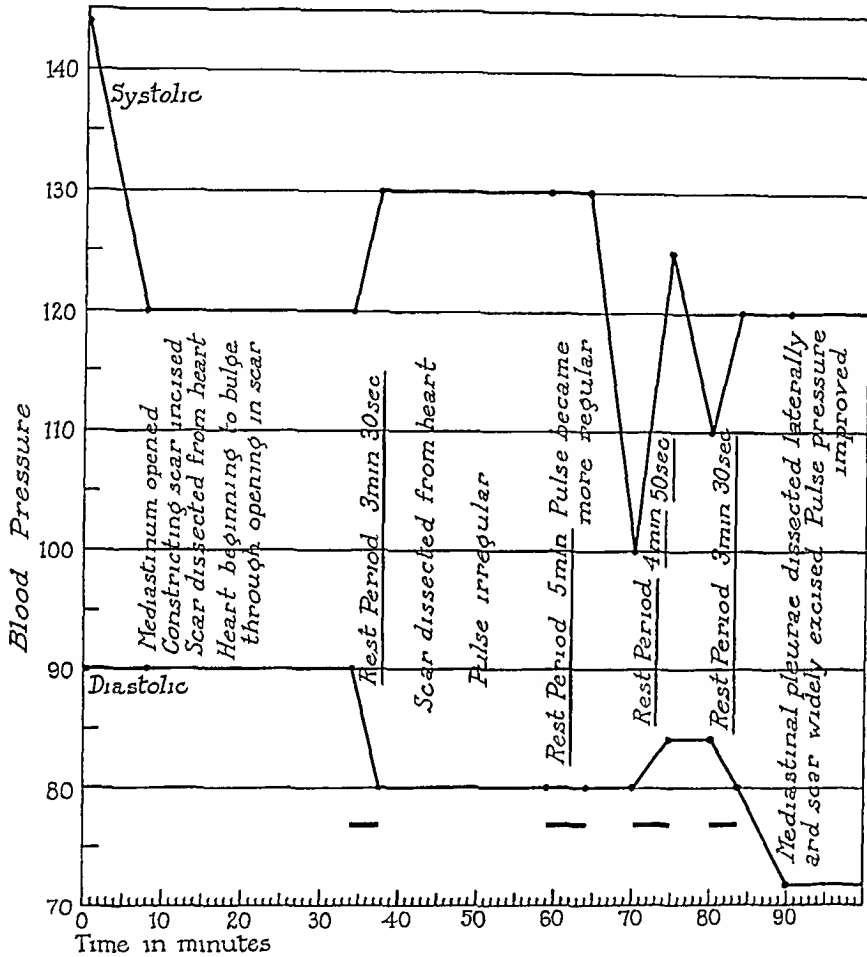


CHART 4—Response of arterial pressure during the resection of a compression scar. Note the beneficial effect of rest periods.

These deleterious reactions from surface stimuli can be controlled in several ways. One suggestion is to avoid producing the stimulus by touching the heart as little as possible. Another suggestion is to give the heart frequent rest periods during the dissection. Another method for the control of reactions produced by surface stimulation is by the use of procaine or metycaine applied to the surface of the heart.² Two cubic centimeters of 5 per cent procaine hydrochloride applied to the surface of the auricles and ventricles is effective in anesthetizing the surface of the heart and blocking the entrance of stimuli. After procaine or metycaine has been applied to the epicardium, surface stimuli are no longer effective in producing extrasystoles. The drug

quiets the heart rate very effectively. Indeed, it can abolish auricular fibrillation when applied locally over the auricles (Chart 5). It is also effective in preventing ventricular fibrillation. We do not mean to imply that the ventricles cannot be thrown into fibrillation after its use, but we have shown, repeatedly, that a minimal stimulus that throws the normal ventricles into fibrillation is not effective after the use of procaine. Metycaine acts much as procaine, but is stronger and more toxic. One cubic centimeter of a 10 per cent solution of metycaine can be safely used. The action of these drugs is

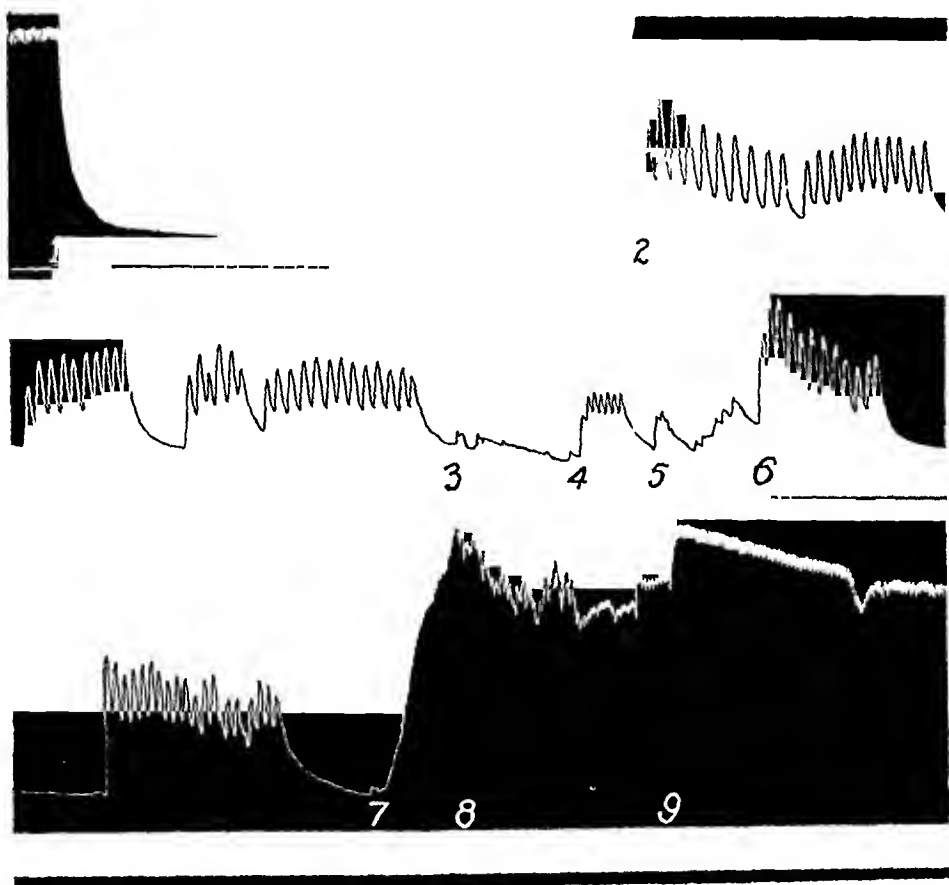


CHART 5—Arterial pressure in an interesting experiment. At 1 the ventricles were sent into fibrillation by a faradic current. At 2 manual massage of the ventricles was carried out. Massage produced a blood pressure which ranged from 40 to 60 Mm of mercury, which preserved the viability of vital structures. At 3, 4, and 5 an electric current was sent through the heart for the purpose of stopping fibrillation. These shocks failed. Massage was continued. At 6 procaine was applied to the heart and at 7 another electric shock of the same strength was sent into the ventricles. This was successful. Note the hypertension produced by the anoxemia. The heart beat is irregular, the auricles continue to fibrillate. At 8 metycaine was applied to the heart and at 9 auricular fibrillation ceased.

not unlike the action of potassium chloride upon the heart. However, procaine or metycaine is more effective without producing the dilated, flabby heart such as results from the use of potassium chloride.

Ventricular Standstill—When the pumping action of the heart ceases and the arterial pressure disappears, the ventricles either come to a complete standstill or they go into incoordinated fibrillary twitchings for a while before every vestige of movement disappears. The fibrillary movements of the ventricles may continue over a period of 15 to 50 minutes (average 24 minutes) in the

anesthetized dog³ Each of these phenomena, ventricular standstill and fibrillation, means death unless something is done to restore a coordinated heart beat

We have had ventricular standstill develop in one human patient during an operation on the heart A compression scar was being dissected from the heart when suddenly the heart stopped A few moments passed without recovery Manual massage of the ventricles was carried out and in a few moments the ventricles began to contract again The heart continued to beat, the operation was completed and the patient recovered During the past 12 years we have seen ventricular standstill develop in an uncounted number of dogs Restoration of the heart beat with recovery occurred as a routine with cardiac massage and the use of epinephrine Epinephrine may be given in two ways when the heart is exposed We usually drip 1 cc of a 1 to 1,000 per cent solution on the surface of the heart If this is not effective in a minute or two, 1 cc of the solution in 10 cc of physiologic solution of sodium chloride is injected directly into the right ventricular cavity Gentle massage is continued about 40 to 50 times per minute When the epinephrine gets into the coronary arteries and into the myocardium, the heart as a rule begins to beat Instead of the restoration of a normal rhythm, the ventricles may be thrown into fibrillation, and when this occurs, an additional problem must be overcome before restoration of the heart beat is possible Large doses of epinephrine may be responsible for the fibrillation However, recovery from standstill is almost always possible when it occurs experimentally at the operating table

It is well known that ventricular standstill is the usual mechanism underlying the transient syncopal attacks of heart block It is also produced by vagus stimulation When the ventricles come to a standstill as a result of disease—pneumonia, myocarditis, *etc*—restoration of the heart beat by massage and epinephrine may be only transient or impossible In recent months we have been having a new experience with ventricular standstill brought about by the use of procaine and metycaine applied directly to the heart This will be discussed under ventricular fibrillation

Ventricular Fibrillation—Ventricular fibrillation is characterized by incoordinated contraction of individual muscle fibers, and the fibrillating ventricles are totally ineffective in expelling blood In our experience, when it occurred in the dog it was always fatal and it always terminated our experiment In the cat the fibrillating ventricles may recover a normal rhythm spontaneously In man ventricular fibrillation is fatal, or almost always fatal It occurs in a number of conditions In electrocution the ventricles as a rule go into fibrillation Experimentally an alternating current applied to the heart readily sets up fibrillation (Chart 5) It is curious that a very strong current may pass through the body and produce ventricular standstill Spontaneous recovery may take place and the ventricles may not go into fibrillation Mechanical stimulation of the heart can produce ventricular fibrillation as can electrical stimulation We have produced it repeatedly by mechanical

stimuli in our experimental work Stopping the epicardium from the heart can produce it

Ligation of a coronary artery can produce ventricular fibrillation In our experience, it always occurred when the common left coronary artery or the left circumflex artery was ligated, and it usually but not always occurred when the descending ramus of the left common artery or the right coronary artery was ligated It always occurred when four or five peripheral branches of the coronary arteries leading to any part of the myocardium were ligated In patients with coronary sclerosis and angina pectoris, ventricular fibrillation is the usual cause of death Contusion of the heart muscle in dogs as well as in human patients can initiate ventricular fibrillation Retraction of the dog's heart can produce fibrillation Chloroform anesthesia can induce it in the human being In general, two sets of conditions bring about ventricular fibrillation One is electrical or repeated mechanical stimuli sent in from the surface of the heart, the other is localized ischemia or anoxemia of the heart muscle It is an interesting point that localized anoxemia seems to be more conducive to ventricular fibrillation than generalized anoxemia of the heart muscle A localized area of anoxic muscle, such as is produced by a contusion or by coronary occlusion (either experimental or in coronary disease), seems to become the focus for impulses that spread over the ventricles and can produce fibrillation Such an area of ischemic heart muscle acts not unlike a trigger zone When the entire heart muscle becomes poorly oxygenated its property of rhythmicity is not so readily destroyed as when the ischemia is localized Generalized ischemia of the heart may be followed by ventricular standstill instead of fibrillation, although the latter may occur

Ventricular fibrillation occurs in many of the sudden cardiac deaths Surgeons sometimes see it at the operating table It has occurred during the use of the electric cautery, especially if the cautery is used near the heart It may occur suddenly during the early stage of anesthesia⁴ We have had it develop in three patients and perhaps it developed in a fourth patient A brief record of these experiences is appended

ABBREVIATED OPERATIVE CASE REPORTS

Case 1—Operation for chronic cardiac compression due to generalized scar tissue around the heart In dissecting the scar from the heart, each pleural cavity was opened Positive pressure was applied by the anesthetist to inflate the lungs The heart suddenly stopped beating Massage and epinephrine did not revive the heart The electrocardiogram taken at the time showed ventricular fibrillation When this operation was performed, we were not prepared to take care of ventricular fibrillation as we are now This patient, we believe, could have been saved

Case 2—The same type of operation was being carried out As the scar was being dissected from the region of the descending ramus of the left coronary artery, the heart suddenly lost its coordinated rhythm and its motion became incoordinated The dissection was immediately stopped and the heart spontaneously became rhythmic again The electrocardiogram proved that the ventricles actually fibrillated This is one of the few cases of ventricular fibrillation in man that recovered The operation was completed and the patient is now living

Case 3—Contusion of the heart had occurred in a steering wheel accident Dilata-

tion and failure of the heart occurred several weeks later. The ventricles suddenly went into fibrillation. The heart was quickly exposed. An electric shock was sent through the heart and the heart was massaged. Recovery was impossible. Mural thrombi were present in the right and left ventricular cavities. Pulmonary emboli were also present. The heart suffered severe intrinsic damage and this might have accounted for the failure of the method to restore rhythm. Procaine and metycaine were not used.

Case 4—This patient had chronic cardiac compression from a generalized scar. The compression as measured by the venous pressure was 45 cm. of water, the highest degree of compression in our series of cases. It was of long standing and the heart necessarily had undergone a marked degree of atrophy of disuse. The scar was easily resected without complication. The atrophic heart was able to pump its increased quota of blood and was able to perform its increased quota of work for eight hours after operation. Then it suddenly ceased to function. The house officer was with the patient at the moment the circulation ceased. He took down the dressing and observed waves of movement over the soft precordium, which he interpreted as coming from ventricles that were fibrillating. We have no electrocardiographic record in this patient to show ventricular fibrillation. It does not make any difference whether the ventricles fibrillated or whether they came to a standstill. In either event, we believe that this heart could be revived today by the application of methods that we have acquired. The work load should have been reduced by venesection so that after the normal rhythm was restored the atrophic heart could carry on.

Methods for the Control of Ventricular Fibrillation—The physiologic studies carried out on this subject are most interesting. The reader is referred to the splendid work of Hooker⁵ and of Wiggers⁶ and of their respective associates. We should like to present a historical review of the subject and give proper credit for the various advances that have been made, but we are unable to do this in this communication. We can give only a few generalizations on the subject. The physiologists have contributed two methods for defibrillation of the ventricles. One method consists of bringing the heart to a complete and absolute standstill with solutions of potassium chloride and then bringing about restoration of normal rhythm by solutions of calcium chloride. The researches centered chiefly on concentration of solutions and on methods of administration. Wiggers emphasized the importance of massage in the method. The purpose of these studies was to make the method practical so that it might be applied to resuscitate people who had been accidentally electrocuted. Realizing that the circulation ceases as soon as the ventricles are thrown into fibrillation, one can appreciate the requirements of success. One requirement is immediate application, *i e.*, within three to five minutes after the electrocution. Insofar as we know, the method has never been successfully applied to a human being. We gave the method a trial in the laboratory and were not sufficiently impressed with the results to see much in the way of practical application even with the heart exposed in the operating room.

The potassium calcium method was rather suddenly superseded by another method. This method consisted of stopping the fibrillary movements by sending an electrical current through the ventricles and then restoring the normal rhythm by massage, a method that was described, in 1899, by Prevost and Battelli.⁷ This method was seen to be superior to the other. In a study of

this method, Hooker, Kouwenhoven and Langworthy⁵ recorded nine failures and 13 successful results, seven of which were transient so that there were only six successful experimental results of a permanent nature out of the 22 experiments. Wiggers subsequently reported 40 successful results out of 47 experimental attempts and makes the point that massage is important before the application of the shock rather than after. We tried the method in the laboratory and found it to be successful in about half of the experiments. We equipped ourselves so that we could use it on the human heart if it should be necessary at the time of operation. A new development then took place in our laboratory, which has made the method uniformly successful. Our failures with the procedure were due to the fact that we could not always stop fibrillation with the electric shock and fibrillation must be completely stopped before one can hope for success.

It was shown by Mautz² that procaine or metycaine applied directly to the heart reduced the irritability of the myocardium very decidedly and that either of these drugs together with the electric shock could uniformly stop ventricular fibrillation. Therefore, we now have a method which in our hands is uniformly successful. We believe that the surgeon should be equipped to use this method. It might come to be applied not only to meet the emergencies occurring during operations upon the heart but also for other sudden deaths occurring with the chest open. It might find application in any sudden death. We have in mind anesthetic deaths, especially from chloroform, and sudden deaths such as occur in status lymphaticus. Perhaps the method can be used in resuscitation of the heart after removal of a pulmonary embolus. The obstacle to success in pulmonary embolectomy is not so much the removal of the embolus and suture of the pulmonary artery as the revival of the heart beat. We believe that a practical development will be made along these lines.

Our Procedure for Defibrillation of the Ventricles—(1) Adequate aeration of the lungs. This is possible only through an intratracheal tube and intermittent insufflation with air and oxygen. This is the first step to be taken and requires preparation and an apparatus. We routinely use an intratracheal tube during our operation of grafting a vascular bed upon the myocardium in patients with coronary sclerosis, so that if ventricular fibrillation should occur, the problem of aerating the lungs is immediately taken care of. The adjustment of the apparatus for aeration must be perfect.

(2) Exposure of the heart and massage of the ventricles about 50 times per minute. This will raise arterial pressure to 40 or 90 Mm. of mercury (Chart 5). It must not be so vigorous as to bruise the myocardium. The central nervous system is now being oxygenated and reflexes return. Restoration of the coronary circulation brings oxygenated blood to the myocardium. Restoration of circulation with oxygenated blood to the brain and to the myocardium is essential. As long as it is carried out, recovery is a possibility even though the ventricles continue to fibrillate. It is possible to continue this artificial circulation over a period long enough to wash out an overdose of anesthetic and long enough for drug effects to disappear. Thus procaine or

metycaine may keep the heart at standstill while epinephrine might precipitate ventricular fibrillation. These drugs gradually lose their effect as massage is carried out. Before the next step is taken two things must be accomplished by the massage. First, the dilatation of the heart must be overcome completely. This is important for success because a dilated heart is prone to keep on fibrillating. Secondly, the heart must have a good color. A cyanotic heart is also prone to keep on fibrillating. When both of these objects are accomplished by aeration and massage, the heart will show slow and coarse fibrillary movements.

(3) An electrode, preferably of silver, measuring about 25 square cm in area, is placed on each side of the heart and an electric current is sent through the ventricles. The electrodes need not be padded to prevent burning if there is a large area of contact with the heart. The current is ordinary alternating current of 60 cycles and 1 to 1.5 amperes*. The duration of the current is short, from 0.5 to about two seconds.

(4) If the shock fails to stop fibrillation (Chart 5), the use of procaine is indicated. Two cubic centimeters of 5 per cent solution are dripped upon the auricles and ventricles. Massage as before until dilatation disappears. Electric shock is usually successful in stopping fibrillation. If it is not, 2 cc of procaine in 10 cc of physiologic solution of sodium chloride are injected into the right ventricular cavity. Massage until dilatation disappears. Electric shock now will stop the fibrillation routinely in dogs.

(5) Every vestige of fibrillary movement must disappear before there is any hope of success. After fibrillation has been abolished and the heart is at a standstill, massage is used. This usually starts a coordinated rhythm. At this place in the procedure, epinephrine may be useful.

(6) After using procaine or metycaine upon the heart, ventricular fibrillation may be converted into ventricular standstill by the current without restoration of any signs of contractility. In this event massage is continued and a solution of calcium chloride is injected into the right ventricle. Wiggers used 5 cc of a 5 per cent calcium chloride solution and 0.1 per cent heparin injected into each ventricle. Hooker and his associates used a weaker solution, 0.046 per cent calcium chloride in 0.9 per cent sodium chloride solution containing heparin and epinephrine. This solution was injected under pressure into the central end of a carotid artery. Arterial injection is not practical on a human patient. Should there be occasion to resort to the use of calcium chloride on the human heart, we would inject 5 or 10 cc of 1 per cent solution into the right ventricular cavity and repeat this if it were necessary.

It is needless to say that throughout the entire procedure, massage of the ventricles is absolutely necessary to preserve the viability of the brain and the myocardium. We have succeeded in reviving hearts that were in ventricular

* "With electrodes applied directly to the heart, currents of 0.4 ampere for five seconds will cause fibrillation and currents of 0.8 ampere or more will stop fibrillation. A current of 0.8 ampere will not induce fibrillation and a current of 0.45 ampere will not stop fibrillation." Quoted from Hooker, Kouwenhoven and Langworthy.⁵

fibrillation or standstill for periods as long as 30 minutes. During this entire period an arterial pressure was maintained by massage of the heart. We have been using this method of defibrillation for several months, and during this period we have fibrillated and defibrillated about 50 hearts with no failures. Many of these were done for purposes of demonstration to visitors during the course of an operation carried out for another purpose. The dogs survive and show no effects of it.

Control of Auricular Fibrillation—In our experimental work, the auricles sometimes went into fibrillation as a result of operative trauma, such as produced by surface stimulation and grasping the auricular wall in a clamp for retraction. It was also seen sometimes when the heart had dilated and the arterial pressure was low. When the ventricles fibrillated, the auricles might or might not fibrillate. Sometimes the auricles continued to fibrillate after the ventricles were thrown out of fibrillation by means of procaine hydrochloride and electric shock (Chart 5). We found procaine efficacious in stopping auricular fibrillation. The drug is applied locally to the surface of each auricle.

This most interesting observation leads us to consider the possibility of treating persistent auricular fibrillation in patients by a surgical method. It may be possible to stop persistent fibrillation (in cases that do not respond to quinidine or digitalis) by altering the irritability of the auricle by changing, in some way, the conduction pathway in the auricles.

Postoperative Considerations—After operation certain alterations in the heart action may be encountered. In the experiments in which the coronary arteries were being occluded, tachycardia, auricular flutter, auricular fibrillation, ventricular extrasystoles or ventricular fibrillation developed. These reactions were carefully observed and it was learned that quinidine sulphate given by mouth definitely reduced these irritability phenomena.² Quinidine sulphate, in doses up to 30 mg per kilogram of body weight, in our animal experiments, given twice a day, has been found to be of definite value in controlling the ventricular tachycardias and presumably has prevented the development of ventricular fibrillation in borderline cases in which the myocardial damage was not too extensive. Our observations on the use of the drug support the clinical use of quinidine sulphate in patients with coronary thrombosis. We give quinidine as a routine to all patients upon whom a heart operation is carried out. A test dose of 3 gr is given in the afternoon before operation. If the patient shows no untoward reaction, 5 gr are given at night, and 5 gr are given in the morning before operation. If there are frequent ventricular extrasystoles after operation, the administration of the drug is continued. In one of our patients auricular flutter suddenly appeared after operation. In this patient digitalis was given intravenously and the flutter promptly disappeared.

We found oxygen to be beneficial after a heart operation. Our cardiac patients are routinely placed in an oxygen tent for several days after operation. To the coronary cases we give 300 cc of 10 per cent glucose intravenously.

after operation. Intravenous solutions are not given to patients with compression because we believe an addition to the circulating blood volume may embarrass further a heart that is already dilated. It would seem advisable in certain cases of compression to reduce the circulating blood volume by venesection. Venesection is indicated in patients in whom the heart has undergone a marked degree of atrophy of disuse. In conclusion we might note that our results insofar as mortality is concerned have definitely improved. We have not had a fatality in the last 17 heart operations.

REFERENCES

- ¹ Beck, C S, and Cox, W V. The Effect of Pericardiostomy upon the Mechanics of the Circulation. *Arch Surg*, 21, 1023-1039, 1930
- Beck, C S, and Isaac, L A. Pneumocardiac Tamponade, a Study of the Effects of Atmospheric Pressure, Negative Pressure and Positive Pressure Upon the Heart. *J Thoracic Surg*, 1, 124, 1931
- ² Mautz, F R. Reduction of Cardiac Irritability by the Epicardial and Systemic Administration of Drugs as a Protection in Cardiac Surgery. *J Thoracic Surg*, 5, 612-628, August, 1936
- Mautz, F R. Resuscitation of the Heart from Ventricular Fibrillation with Drugs Combined with Electric Shock. *Proc Soc Exper Biol & Med*, 36, 634, June, 1937
- ³ Wiggers, C J, Bell, J R, and Paine, M. Studies of Ventricular Fibrillation Caused by Electric Shock. II. Cinematographic and Electrocardiographic Observations of the Natural Process in the Dog's Heart. Its Inhibition by Potassium and the Revival of Coordinated Beats by Calcium. *Am Heart J*, 5, 351-365, 1930
- ⁴ Guedel, A E, and Knoefel, P K. Ventricular Fibrillation in Anesthesia. *Am J Surg*, 34, 496-499, December, 1936
- ⁵ Hooker, D R. On Recovery of the Heart in Electric Shock. *Am J Physiol*, 91, 305-328, December, 1929
- Kouwenhoven, W B, Hooker, D R, and Langworthy, O R. The Current Flowing Through the Heart Under Conditions of Electric Shock. *Am J Physiol*, 100, 344-350, 1932
- Hooker, D R, Kouwenhoven, W B, and Langworthy, O R. The Effect of Alternating Electrical Currents on the Heart. *Am J Physiol*, 103, 444-454, February, 1933
- Hooker, D R, and Kehar, N D. Carbohydrate Metabolism of the Heart During Ventricular Fibrillation. *Am J Physiol*, 105, 246-249, 1933
- Kehar, N D, and Hooker, D R. Evidences of an Altered Tissue State in Ventricular Fibrillation. *Am J Physiol*, 112, 301-307, 1935
- ⁶ Wiggers, C J, and Associates. Studies of Ventricular Fibrillation Caused by Electric Shock. I. The Revival of the Heart from Ventricular Fibrillation by Successive Use of Potassium and Calcium Salts. *Am J Physiol*, 92, 223-240, 1930
- Wiggers, C J, Bell, J R, and Paine, M. Studies of Ventricular Fibrillation Caused by Electric Shock. II. Cinematographic and Electrocardiographic Observations of the Natural Process in the Dog's Heart, Its Inhibition by Potassium and the Revival of Coordinated Beats by Calcium. *Am Heart J*, 5, 351-365, 1930
- Wiggers, C J, Theisen, H, and Shaw, H D B. Studies on Ventricular Fibrillation Produced by Electric Shock. III. The Action of Antagonistic Salts. *Am J Physiol*, 93, 197-212, 1930
- Wiggers, C J. Cardiac Massage Followed by Countershock in Revival of Mammalian Ventricles from Fibrillation Due to Coronary Occlusion. *Am J Physiol*, 116, 161, 1936
- ⁷ Prevost, J-L, and Battelli, F. Sur quelques effets des décharges électriques sur le

cœur des mammifères Comptes Rendus des Seances de L'Academie des Sciences,
129, 1267, December 26, 1899

DISCUSSION —THE PRESIDENT, DR EVARTS A GRAHAM (St Louis) This very beautiful work of Doctor Beck's, only a small part of which he exhibited to us this afternoon, is contributing a very important chapter, I think, not only to physiology, but to clinical medicine and surgery as well

Those of us who are interested in thoracic surgery particularly notice some of these deleterious effects on the heart which Doctor Beck has described here this afternoon, not only when operations are performed on the heart itself, but sometimes, for example, when in performing difficult operations in the thorax, particularly in the left thorax, it becomes necessary to get the heart out of the way in order to have better exposure

I, at least, and I think that probably all of us who do a good deal of work in this field, notice occasionally some of these very serious effects which Doctor Beck has described We have likewise noticed that if the operation is stopped momentarily, particularly if the retraction is stopped and the heart is given a rest period for a few minutes, and if this is repeated from time to time, the operation can often be transformed from an exceedingly dangerous one, which may prove fatal on the table, to one which will be well tolerated by the patient, and from which a perfectly normal recovery may be expected to occur

I should like to ask Doctor Beck one question myself before throwing his paper open to general discussion, and that is whether or not he ever finds fatal cerebral embolism after massage of the heart that he demonstrated this afternoon in the moving pictures

DR CLAUDE S BECK (Cleveland, Ohio) closing I can only say, Doctor Graham, that we have an uncounted number of dogs in the laboratory whose hearts have been fibrillated and defibrillated, and they appear to be normal We have no evidence of cerebral embolus I must confess that we have not looked particularly for emboli, but the dogs are active and they seem normal

We have lost three or four patients from ventricular fibrillation The discussion of these patients will be found in the article submitted

FOREWORD
TO
SYMPOSIUM ON CANCER

EVARTS A. GRAHAM, M.D.

PRESIDENT OF THE AMERICAN SURGICAL ASSOCIATION

THE committee in charge of the program felt that the developments in cancer have been so startling within the last few years, and are still showing promise of developing with perhaps an even more rapid rate, that it was decided to devote an entire day to a consideration of cancer, not only to its practical therapeutic aspects, but also to some of the newer developments concerning the etiology of cancer, which of course are most remarkable. We felt that in order to get an authoritative opinion concerning some of the more recent, practical aspects of cancer, we should like to have some of the outstanding world authorities here as our guests. Accordingly, we invited Professor Henri Coutard of the Curie Institute, Paris, and Mr. Geoffrey Keynes of St. Bartholomew's Hospital, London, to come and address us.

THE ETIOLOGY OF CANCER IN THE LIGHT OF OUR PRESENT KNOWLEDGE

JOHN J. MORTON, M.D.

ROCHESTER, N. Y.

FROM THE DEPARTMENT OF SURGERY, THE UNIVERSITY OF ROCHESTER SCHOOL OF MEDICINE AND DENTISTRY,
ROCHESTER, NEW YORK

MALIGNANT disease has been recognized and studied since the dawn of medical history. Keen observers from time to time called attention to the association of cancer with certain occupations. Thus Percivall Pott¹ noted that cancer of the scrotum occurred in chimney sweeps. Gradually there developed a knowledge that some occupations carried a definite cancerous hazard for those engaged in them. This list of industrial and occupational cancers has grown to quite considerable proportions. Although promising leads were thus available from the study of cancer as it occurred naturally in the human race, the greatest advances in our understanding of the cause of cancer came with the experimental production of it in animals.

Knowledge regarding the cause of cancer came to us from several sources. The human family furnished examples of cancer in its natural origins. It gave us evidence of the influence of constitution, race and environment. The potency of environmental factors was shown when man produced human cancer, unwittingly to be sure, but effectively, in many of his occupations. Naturally occurring cancers in many species of the animal kingdom added to this information. The artificial transfer of cancer to other animals of the same species gave possibilities for controlled observations. Hereditary influences could be more easily recorded in selected animal strains of known constitution. And finally when cancer could be produced at will in various species of animals, a method was provided to test the cancer promoting powers of many different substances.

The attempt to glean from the literature the salient facts regarding the cause of cancer is a task which is well nigh impossible for any one individual. It presupposes that such an individual be conversant with such diverse subjects as heredity, biology, chemistry, pathology, metabolism, radiant energy, vitamins, viruses, enzymes and the internal secretions of the ductless glands. The limitations imposed by such a formidable array accordingly must be taken into account. In addition to this, the possibility that one single agency should furnish the cause for the many diverse types of cancer is remote. However, the ultimate intercellular change promoted by the varied cellular incitants may well be the same type of reaction.

Inciting Factors—The cancerous change in the cell may be initiated by many different forms of inciting factors. It is possible to classify these agents under three main groups.

- (1) Physical
 - a Traumatic
 - b Thermic—cold, heat
 - c Actinic—ultraviolet, roentgen rays, radium
 - (2) Chemical
 - a Stasis
 - b Simple chemicals
 - c Coal tars
 - d Internal secretions—estrogens, vitamins
 - (3) Biologic
 - a Bacteria
 - b Viruses
 - c Helminths
- Combinations of (1), (2) and (3)

The evidence that these inciting factors may operate in the production of malignancy has been gathered (a) from human occupational cancers^{2 3 4, 5} (Table I), and (b) from studies on the origin of cancers in the human in association with the presence of these physical, chemical or biologic agents, (for example, the well known Kangri cancer of the skin of the abdominal wall and inner sides of the thighs resulting from burns received in squatting over the basket braziers, the betel nut cancer of the cheek in the Far East, the liver cancers associated with fluke infestations, the jagged tooth, syphilis and cancers of the mouth, the cancers arising in scars and ulcers^{6 7 8}, the effect of sunlight on the skin^{9 10}, the arsenic cancers¹¹, the rôle played by helminths¹² in human tumors, the endocrine factor in breast cancer¹³, and the estimation of how much weight should be given to single traumas¹⁴), and (c) from the experimental laboratories of the world where cancers have been produced in various species of animals by diverse carcinogenic agents

TABLE I
INDUSTRIAL AND OCCUPATIONAL CANCERS

Occupation	Inciting Agent	Site	Author	Date
Chimney sweep	Soot	Scrotum	Pott	1775
Copper smelter	Arsenic	Scrotum	Paris	1820
Coal tar distiller	Tar, paraffin	Scrotum	V Volkmann	1875
Miner (cobalt)	Dust (arsenic, cobalt, bismuth (?))	Lung	Harting and Hesse	1879
	Radium emanation (?)			
Aniline dye workers	Fuchsin (?) (probably β -naphthylamine, possibly benzidine)	Bladder	Rehn	1895
Roentgen ray workers	Roentgen rays	Exposed skin Hand	Frieben	1902
Mule spinners	Oil	Scrotum	Southam and Wilson	1922
Paraffin workers	Shale oil	Skin	Scott	1923
Radium dial painters	Radium, mesothorium	Bone	Martland	1931
Outdoor workers	Sunlight	Skin	Many	Years
Roentgen ray workers	Radiation	Lymph nodes	Many	Since
Radium workers		Bone marrow		1900

Before 1916, the experimental production of cancer in animals was practically impossible. Clunet¹⁵ is credited with the induction of cancer in rats by long exposures to roentgen rays. Fibiger's¹⁶ well known experiments by which he produced cancer of the stomach in rats which harbored an encysted worm parasite also preceded the classical tar painting experiments of the Japanese investigators.¹⁷ But the investigations of Ichikawa and Yamagiwa¹⁷ only 20 years ago launched an intensive program of experimental cancer research all over the world. In the succeeding 15 years, 700 papers appeared in the literature dealing with the production of tumors by tar and tar products of unknown chemical formulae. During the same period, cancer was produced by many other different agents of physical, chemical and biologic nature. To select a few of these will serve to emphasize this side of the problem. Leitch¹⁸ placed human gallstones in the gallbladders of guinea-pigs, and cancer resulted after sufficient time had elapsed. Bagg¹⁹ caused carcinoma to follow stagnation of the breast secretions by repeatedly breeding without allowing the mice to suckle their young. This result was also brought about by ligation of the nipples. Berenblum²⁰ by successive short applications of carbon dioxide snow to the skin of mice had carcinomata develop at the site of injury. This work was confirmed by Mansens,²¹ Roffo,²² Findlay,²³ Putschar and Holtz,²⁴ and Herlitz, Jundell and Wahlgren²⁵ were among those who produced carcinomata and sarcomata in rats and mice following long exposures to sunlight or ultraviolet light. Daels,²⁶ over a number of years, succeeded in causing sarcomata and carcinomata in mice, rats, and guinea-pigs by the introduction of glass tubes or collodion covered threads which contained radium solutions or salts. Biltz²⁷ placed small amounts of radium element in collodion sacs in the liver or kidney of guinea-pigs with resulting sarcomata of the kidney, carcinomata of the bile passages, and malignant unidentified tumors of the spleen. The malignancy of these growths was evidenced by wide metastasis. Petrov and Krotkina²⁸ put both empty and radium containing glass tubes into the gallbladders of guinea-pigs and had cancers grow equally in the control and radiated groups. Lacassagne²⁹ caused sarcomata and carcinomata in rabbits by irradiating by roentgen rays either infected or sterile inflammatory foci. Ludin³⁰ using roentgen rays caused osteogenic sarcomata in adult rabbits. Schurch and Uehlinger³¹ used radium needles or mesothorium in Vaseline with direct implantation to cause osteogenic sarcomata in rabbits. Sabin, Doan and Forkner³² succeeded in getting osteogenic sarcomata in rabbits by intravenous injections of radium chloride and mesothorium. Bullock and Curtis³³ produced sarcoma in the liver of rats by feeding them the eggs of the cat tapeworm. The malignant tumors developed in the fibrous tissue of the cyst walls, the rat serving as an intermediate host. These sarcomata proved to be very malignant and transmissible by inoculation. This furnished research laboratories with an excellent experimental material. Cancers have been noted to arise after long continued applications of heat, of simple acids, of simple alkalis. Cancer

is claimed to have been initiated by various bacterial agents (Blumenthal, Glover), though this work has failed of confirmation by other expert workers

There has been a great revival of interest in the etiologic factors due to the brilliant researches upon the chemistry of the coal tars Kennaway³⁴ had worked for several years on the crude pitches, oils, and tars as carcinogenic agents He concluded that the carcinogenic principle must be among the unknown compounds in the coal tar, and that these compounds had remained unknown because they were unstable or in only minute quantities It was known at that time that several hundred substances had been identified in coal tar, though only approximately 100 had been isolated from it³⁵ Accordingly, the chance of selecting the proper agent seemed impossible Mayneord had applied the fluorescence spectrum to this problem Hieger, another member of Kennaway's group, became interested Kennaway and Hieger published several papers upon the spectra of tars and oils^{36, 37 38} In 1929, a German chemist Clar³⁹ described a method for the synthesis of 1 2 5 6 dibenzanthracene Hieger had previously noticed the resemblance between the fluorescence spectrum of benzantracene and that of one of his carcinogenic fractions of coal tar Consequently, he was on the lookout for pure chemical substances of this nature to test their potency as carcinogenic agents The alert, prepared mind was thus ready to make use of the purified chemical substance When 1 2 5 6 dibenzanthracene was painted on the skin in a benzene solution, cancers were produced in mice⁴⁰ A subcutaneous injection of the same substance in lard caused sarcomata in mice and rats⁴¹ The fluorescence spectra of active carcinogenic tar fractions showed bands at wavelengths 4,000, 4,180 and 4,400 angstroms By tracing the appearance of these bands in successive fractional distillations and testing the carcinogenic potencies, Cook, Hewett and Hieger⁴² were able to identify and isolate 1 2 benzpyrene from the coal tar The numbering has been changed to 3 4 benzpyrene to conform to older usage in the literature This is the only potent carcinogenic compound which has been shown to be present in coal tar⁴³ In its first isolation, 1 2 benzpyrene represented about 0.003 per cent of the original coal tar pitch Cook⁴⁴ noted that the phenanthrene ring system was common to practically all the carcinogenic hydrocarbons But more important still, he suggested that this chemical group occurred in the sterols, the estrogenic hormones, the male hormones, and vitamin D Many other chemical substances have been tested for their cancer producing properties While certain others have been found with varying potencies—triphenyl benzene, tetra-phenyl methane,⁴⁵ o-aminoazotoluene,⁴⁶ styryl quinoline,⁴⁷ etc, the benzantracene group still constitutes the most important group of carcinogenic chemicals An excellent presentation of this subject has been given by Cook, *et al*⁴³ Improved methods for the synthesis of these potent hydrocarbons have rapidly followed

It was a natural step to attempt to produce a cancer-potent chemical as a degradation product of some normally occurring body constituent Consequently when the bile acids were split into cholantracene, which has proved

to be a powerful carcinogenic agent, the possibility of such a natural evolution in the human body must be admitted ⁴⁸

Even more striking has been the production of mammary carcinoma in mice by continued stimulation of these glands by a normal hormone. Leo Loeb⁴⁹ for years has furnished evidence of the effect of the ovaries on mammary cancers in mice. His experiments proved that the presence or the absence of the ovary determined the frequency of mammary cancer and the age at which it appeared. Malignancy was further conditioned by hereditary factors. Lacassagne⁵⁰ injected massive daily doses of estrone benzoate in mice. He thus kept the mammary glands under continuous stimulation by a physiologic agent. He was able to show a progressive change of the breast through various stages to malignancy. This result could also be brought about in male mice of a strain in which the females showed a high natural incidence of breast cancer. Estrone seemed to act selectively on tissue connected with the genital apparatus as it produced changes in such other organs as the vagina, uterus and prostate. An exception was noted in that the bladder epithelium also showed changes when there was retention of urine. This work was confirmed on male mice by Gardner, Smith, Allen and Strong.⁵¹ When estrin has been applied to the skin of mice for long periods, the effects were not on the local skin but on the tissues connected with the genital structure—breast, vagina, uterus in females, prostate in males.⁵² A comparative study of other estrogenic hormones was also carried out by Lacassagne,⁵³ who demonstrated characteristic tissue changes in the mammary glands, uterus, prostate and hypophysis. Each hormone showed some effects which differed from those provoked by the others. The close similarity in chemical structure between the carcinogenic hydrocarbons and the estrogenic substances received also a proof of similar physiologic action when it was found that some of these hydrocarbons could induce estrius.⁵⁴ An excellent review on estrogenic hormones and carcinogenesis has been presented by Leo Loeb.⁵⁵ In a comprehensive review, Taylor¹³ claimed that he could find no clinical evidence as yet of any specific endocrine dysfunction as a cause for human breast cancer. Evidence for the participation of other ductless glands in the genesis of cancer has not been so pronounced. It has been known, however, that many of these glands have interlocking relationships in the control of growth processes. Michalowsky⁵⁶ furnished indirect evidence of the action of a male hormone by the experimental production of teratoma testis in roosters. When zinc chloride in 5 per cent solution had been injected into the testes of his birds, teratomata developed, but only in the spring when the gonadal activity was at its height. Bagg⁵⁷ was able to produce teratoma testis at any season by stimulating the testis over long periods with hormones from the anterior lobe of the pituitary gland. The hormone alone could not bring about this effect. Ferguson⁵⁸ studied a series of human testis teratomata. He concluded that it seemed as if the embryonal types required prolactin A as an essential to growth. On the other hand, when large doses of prolactin

were used by Zondek, *et al*,⁵⁹ in mice with transplanted Ehrlich mouse cancers these growths were slowed. A similar retardation of growth was demonstrated by Duran-Reynals⁶⁰ against the Brown-Pearce rabbit cancer. This resulted when the tumor was mixed with a testicular extract—presumably a male hormone effect.

The increased production of hormonal secretions by various tumors of the thyroid, adrenal, parathyroid, islands of Langerhans, *etc*, with demonstrable alterations in physiology, focused attention on this phase of the problem. Multiple cystic disease of bone has been reproduced experimentally by an oversupply of parathormone^{61, 62}. This condition, however, is merely a physiologic one which can be reversed by withdrawal of the stimulus. So far as I am aware, no malignant tumors have been produced experimentally by any of these internal secretions.

Some recent experimental work upon vitamin factors has been of extreme interest. Adamstone⁶³ destroyed vitamin E in the diet fed to developing chickens. There resulted lymphoblastomata involving the heart, lungs, liver, spleen, pancreas, and gizzard in a large proportion of the experimental animals. In contrast to this, Rowntree, *et al*,⁶⁴ administered vitamin E to white rats in the form of an ether-extracted crude wheat germ oil. After 1 cc had been given in the food daily for 116 days, spindle cell sarcomata of the abdominal cavity were found. These could be transplanted to other animals. The neoplasms grew rapidly and caused death. Repetition of this work by Dorrance and Ciccone⁶⁵ showed tumors in 100 per cent, transplantable in 100 per cent. Other oils and purified wheat germ oil gave negative results. Other papers hinting at an indirect effect through the diet were written by Watson and Mellanby,⁶⁶ and Bittner.⁶⁷ The former believed that addition of a high proportion of butter induced a fatty condition of the skin (agreement with Roffo), the latter, simply that improved general health caused more animals to live to the cancer age period.

It has been known for years that viruses can be provocative agents for the neoplasms of fowls. In 1911, Rous⁶⁸ demonstrated that chicken tumor No. 1 could be transmitted by a cell free filtrate. Murphry⁶⁹ succeeded in transferring it with desiccates in the same year. Fowl leukemia was transmitted by means of cells and cell free filtrates as early as 1908.⁷⁰ Since then many neoplasms of fowls have been investigated. Over 27 tumors, mostly sarcomata, have been studied. Most of the malignant tumors of fowls have been found to be transmissible by cell free filtrates and desiccates. Comprehensive reviews on the transmissible tumors of the fowl and on the nature of viruses have been made by Claude and Murphy⁷¹ and Rivers,⁷² respectively. Research workers were greatly agitated when these discoveries were first announced. The solution of the puzzle of the etiology of cancer seemed to be at hand. But it was not so simple. The mammalian tumors did not yield a filterable agent, the carcinomata, also, did not behave well in this respect.

Recently interest has been aroused again by the discoveries of cell free

transmissible papillomata and fibromata in rabbits^{73 74} Rous and Beard⁷⁵ experimented with the Shope rabbit papilloma virus. It was found that in the course of a few months many of these virus-induced papillomata became malignant squamous cell carcinomata. The virus could not be recovered from the cancers but evidence of its presence was obtained indirectly by serologic tests. When the virus was injected into the blood stream of rabbits with tarred ears, it localized and caused both papillomata and cancers to develop at once⁷⁶. Berry and Dedrick⁷⁷ killed the virus of infectious myxomatosis of rabbits by heat so that it was no longer effective in producing the disease. They then mixed this inert myxomatous material with the benign virus-transmitted Shope fibroma of rabbits and transformed it into a malignant myxomatous growth. Recently a filter passing agent was shown to be associated with a cancer of the kidney in the leopard frog⁷⁸—*Rana pipiens*.

Evidence that the same cell free transmissible agents in fowls may be effective in eliciting a number of different histologic responses has been reported by several workers. Oberling and Guérin⁷⁹ have seen the agent of Rous' sarcoma produce leukemia, as also that for the Murray-Begg endothelioma. Meyer and Engelbreth-Holm⁸⁰ described erythroblastosis and sarcoma in their animals in response to the same agent. In Furth's series,⁸¹ leukosis, sarcoma, endothelioma and fowl paralysis—all due to filterable substances—were recorded as following injection of one such agent. Troisier⁸² showed that the leukosis and sarcoma responses were interchangeable. These observations may furnish support to the contention that viruses of different types reside harmlessly in the cells of the body much the same as bacteria in the intestinal tract.

It was discovered that tumors in fowls could be induced by the injections of coal tar. At once a search was instituted to find out whether these chemically induced fowl tumors could be transmitted by a cell free filtrate. McIntosh⁸³ claimed that he found such a property in the tumors of three fowls. Peacock,⁸⁴ in a very careful study on a large number of birds, was unable to confirm this. Murphy and Landsteiner,⁸⁵ and Sturm and Murphy⁸⁶ had previously been unsuccessful. Murphy, *et al*,⁸⁷ obtained purified solutions of chicken sarcomata which were cell free and protein-free yet carried the active agent. Margaret Lewis⁸⁸ confirmed this work. Andrewes⁸⁹ claimed that the virus might still be present in tar tumors but not demonstrable by filtering. He called attention to the fact that occasionally the Rous virus cannot be filtered, that the Mill-Hill fibrosarcoma of fowls was cultivated for three years before it could be filtered, and finally he showed that pheasants which had been inoculated with a hitherto nonfilterable tar induced sarcoma of the fowl, all developed antibodies which would neutralize the virus of Rous sarcoma No. 1. Normal pheasants had never demonstrated this ability. Parsons⁹⁰ believed that she transmitted by cell free filtrations a few sarcomata which had been induced in mice by injection of coal tar hydrocarbons. The whole virus relationship to tumor

growth has been a very complex one. Reviews of this subject by Andrewes⁹¹ and Rous⁹² should be consulted.

In contagious lymphosarcoma of the dog all the characteristics of a true tumor have been elicited. It can be transplanted to practically all normal dogs by living tumor cells. An agent cannot be separated from the cells. The condition can be transmitted by direct contact from the sexual organs where it occurs as a primary disease. In this respect it seems to be a highly contagious venereal disease. The tumor cells seem to be transferred directly to open ulcerating areas.⁹³

Common characteristics which can be demonstrated from the interaction of these inciting agents upon the cell in the production of cancer can be summed up briefly as follows:

Every potentially growing cell can be made to undergo neoplastic change (Ewing first called attention to malignancy as a universal cell potentiality.)

Differentiated tissues must first undergo disorganization before acquiring growth qualities.

The action of the inciting agent must be long continued and unremitting (The viruses offer an exception to this.)

The inciting agent must injure but not destroy the cells.

The same inciting agent may initiate neoplastic change in different types of cells. Depending upon the type of cell with which the agent comes in contact, chance appears to be an important factor in the histologic type of neoplasm produced.⁹⁴

Species differences in cellular response must be explained by possession of cell resistance or cell susceptibility probably on the basis of hereditary constitution.

Carcinogenic action of these inciting factors cannot be explained as simply due to chronic irritation. All irritants do not produce cancer.

Time of action of the inciting factor is important, not age of the animal per se.

Specific endocrine substances seem to have a more pronounced effect against the tissues upon which they normally act as a stimulus.

When there has been a certain summation of action upon the cell, the change produced in it proceeds inexorably regardless of whether the inciting factor is withdrawn.⁹⁵

The inciting factors act upon the cells to set off an intracellular mechanism which is handed down to all future cell descendants.

When this mechanism has been provoked the inciting agent is no longer necessary.

The fundamental cause of cancer is an intracellular change which becomes self-perpetuating.

We will now turn to a consideration of this phase of the problem.

The Fundamental Change—All students of the cancer problem agree that the inciting agents bring about an intracellular change which is the process of importance. It constitutes the malignant change. Although it

has become possible to induce this malignant change at will by an increasing number of carcinogenic agents, the nature of the malignant change still remains baffling. There is nothing which the microscopist can identify with certainty as the beginnings of this change. This change from an orderly pattern to one without regulation is self-perpetuating. All the cells descended from those showing the malignant change retain the same qualities. They almost invariably reproduce the same histologic structure and breed true to type. This has been observed in transplantable neoplasms which have been carried in experimental animals for 30 years. Factors which bear on the behavior of the cell under impact from the inciting agents may be biologic or chemical in nature. It thus becomes necessary to take into consideration the effects of the hereditary constitution, the internal cell metabolism, changes in the chemical balance which influence cell growth, and the virus problem.

Evidence that the hereditary constitution has a bearing on the cancer problem comes from several directions. Existing human cancer statistics and records have very little value because of many inherent errors. But the accurate study of cancerous families may be of value. This is especially true where a study is made of specific organ types of cancer in relation to families.⁹⁶ And when families have a certain sort of tumor which is not common, the familial incidence becomes significant.⁹⁷ It is generally accepted that certain tumors have a tendency to appear in certain families. Glioma of the retina, multiple neurofibromatosis (v. Recklinghausen), multiple cartilaginous exostoses, and multiple polyposis of the intestine are well known examples of tumors which have a decided family incidence. The list might be extended to cover multiple benign cystic epithelioma, xeroderma pigmentosum, and hereditary telangiectases. There are three possibilities: (1) That the tumors themselves are inherited—the offspring having the neoplasm *ab initio*. This is exceedingly rare but some congenital tumors are known. (2) That a tendency towards the innate condition is transmitted. (3) That a reduced resistance to those factors causing tumor formation is handed down.⁹⁸ The two latter types would probably be referred to by most writers as increased susceptibility and diminished resistance. According to some geneticists, these terms are really an expression of the amount of inciting factors and the length of time through which they act. Additional evidence on the human heredity factors can be supplied by a study of the neoplasms arising in identical twins.^{99, 100} These individuals possess the same hereditary pattern. In some cases there have been simultaneous and symmetrical occurrences of similar tumors in each one of the pair. These cases furnish striking evidence of the similarity in hereditary cell response. In other cases the appearance of the neoplasm in one of the pair may be delayed, or it may never arise. Such instances serve to illustrate the importance of inciting or environmental factors in contrast to the constitutional ones.

The most important way to study the factors of cell inheritance is

through animal experimentation Tyzzer¹⁰¹ and Murray¹⁰² were among the first to note that spontaneous breast cancers tended to have a familial distribution in their stocks of mice. This was confirmed by Leo Loeb and Lathrop¹⁰³ who segregated families of mice in breeding experiments. Maude Slye¹⁰⁴ demonstrated that cancer not only ran in families of mice but that a tendency to specific types was definitely inherited by certain strains. She concluded that the tendency to develop cancer was a unit recessive character handed down in inheritance. Little¹⁰⁵ was the first to insist that strains with genetic uniformity be used for this work. These strains could be produced by close inbreeding of brother to sister or progeny to parents. The variants were in this way reduced and the strains became homogeneous. Pedigreed tested strains of high and of low spontaneous neoplasms were in consequence available for experimentation. By crossing such strains a hybrid strain was provided which showed a large number of cancers—disproving the unit recessive character of Slye. Matings of females from high breast cancer strains with males from low cancer strains gave hybrids in which the females showed spontaneous breast cancer proportional to the strain from which the female parents were derived. If the males from the same high strain were crossed with low strain females the incidence of spontaneous breast cancer in the hybrids was greatly diminished. This type of inheritance followed the maternal line and was nonmendelian in character. It established the existence of genetic influences outside the chromosomes. It has been shown beyond question that in heredity mammary and nonmammary tumors differ in many important respects. The formation of mammary tumors is, to a large extent, dependent upon the interplay between constitutional and internal secretory, *i.e.*, environmental factors¹⁰⁶. There is a definite relationship between the amount of breast tissue and the functioning of the ovary as previously discussed in the castration experiments of Loeb⁵⁵. This point received a striking confirmation in the experiments of W. S. Murray¹⁰⁷. He showed that castrated male mice of a high female breast cancer strain could be made to develop cancer of the breast when ovaries had been successfully implanted in them. The work of Lacassagne⁵⁰ also bore this out. That the constitutional factor must also be considered is proved by the experiments of Fekete and Green¹⁰⁸. In a genetically susceptible strain, blockage of the mammary ducts with milk stagnation was influential in determining the site and time at which mammary tumors appeared. But the same measures did not cause tumors in hereditarily resistant animals which ordinarily did not develop such tumors. Bagg¹⁰⁹ was able to mask the extrachromosomal influence described above by subjecting the mammary glands of the hybrid strain to abnormal ovarian stimulation. This was done by rapid breeding and nonsuckling. This procedure combined with selective breeding may make it possible to further standardize high and low tumor strains.

In a study of the genetic aspects of mouse leukemia MacDowell¹¹⁰ noted that the incidence of leukemia was quite different if the transmission was

from the male or from the female. Since the chromosomal mechanism is shared by fathers and mothers alike, the implication is clear that besides the familiar chromosome transmission, there must be some nonchromosomal mechanism. Clara Lynch¹¹¹ proved that different strains of mice reacted quite differently in their susceptibility to tumors, both spontaneous and tar induced. Susceptibility seemed to be organ specific, chemically induced lung tumors appearing in higher proportions in those strains which had a high spontaneous lung tumor incidence. Dunning, Curtis and Bullock¹¹² produced tumors in mice and rats of different genetic strains by injections of dibenzanthracene and benzpyrene in one or more loci. Many histologic types of tumor were produced by these agents. They concluded that the occurrence of malignancy was a universal cell characteristic—that the histogenesis depended upon the fortuitous exposure of the various types of cells to the irritant, and that the occurrence of malignancy was not influenced by age, sex or genetic constitution.

The development of certain tumors in heredity experiments has been reported in the biologic literature. Stark^{113, 114} discovered a malignant melanoma of the fruit fly. It was sex-linked and lethal, killing one-half the males. Another benign not sex-linked melanotic tumor was also described. These tumors have been carried on by inbreeding for 17 years. Gordon¹¹⁵ developed general melanosis with tumor-like growth in hybrids of Mexican killifishes. The macromelanophores were heritable, sex-linked and dominant.

From this partial review on the influence of heredity the following summary may be made:

The laws of genetics are quantitative and statistical.

To satisfy their requirements it is necessary to deal with large numbers.

The strains used should be as pure and as free of variables as possible.

The hybrids from these strains can then be analyzed.

Factors can be sorted out and manipulated by backcrossing breeding experiments.

Human statistics are inaccurate, incomplete and unsatisfactory.

The numbers are generally too small to be significant.

Well kept family records with high tumor incidence may be useful, especially for specific types at specific age periods.¹¹⁶

The occurrence of rare types of tumors in the same family indicates a hereditary influence.

Some types of new growth are known to have a familial incidence—multiple exostoses, polyposis, xeroderma, *etc*.

Identical twins should furnish ideal material for the study of constitutional factors.

Inciting (environmental) factors may accentuate the speed of a reaction destined to occur at a later date.

Study of experimental heredity in animals has revealed strains of high and of low cancer incidence.

Specific types of cancer seem to have definite familial relationships

The tendency to develop cancer appears to be organ specific

Under ordinary conditions of life, development of spontaneous tumors follows a well defined pattern

Extrachromosomal influences on neoplastic development can be demonstrated by noting differences in lines descended from the male or female side of a known genetic strain

Identification of the internal secretion of the ovary as such an extrachromosomal factor has been proved for breast cancers

Susceptibility and resistance to cancer must be multiple factors in inheritance

Susceptibility to development of neoplasm can be hastened by application of inciting agents

Extrachromosomal factors can be masked by the application of strong inciting factors

Strains resistant to the spontaneous development of cancer can be overwhelmed by a strong stimulus and made to produce cancer

In this sense resistance and susceptibility are relative terms

Cancer is not handed down in heredity as such Cellular susceptibility or resistance to environmental factors are probably the mechanisms concerned

The cancerous change is thus probably the result of an interplay between constitution and environment

Inherited susceptibility to cancer may never appear if the individual is protected from adverse environmental stimulating factors, or if the proper age period is not attained

Inherited resistance to cancer can be broken down by the application of repeated strong inciting factors, as is to be noted in the case of roentgen rays, occupational cancers, *etc*

The studies of Warburg¹¹⁷ apparently opened a promising new lead in the study of the fundamental intracellular change which had taken place in cancerous growths The demonstration that cancer cells possessed a mechanism that allowed them to split up sugars in the absence of oxygen was arresting When he added the information that there was also a marked quantitative difference in the ability to use sugar a great advance seemed imminent These properties were soon found to be present in most actively growing normal cells In some tissues such as the retina, these chemical changes were a normal mechanism Furthermore, in some neoplasms these characteristics were absent Such results caused investigators to proceed cautiously in this field A great deal more study can be profitably put on this phase of the question

Investigators have been interested in tissue stimulators and inhibitors as possible factors in the production and the control of neoplasms for several years Among these studies, those of Burrows, of Waterman, of Chambers and Scott have been consistent and of high quality Murphy and his co-

workers¹¹⁸ began to extract fowl sarcomata in an attempt to separate inhibiting factors. Such an agent was found. It was capable of neutralizing the causative agent of fowl sarcomata but was also potent against the growth of transplantable mouse sarcomata¹¹⁹. This showed that the inhibiting substance was not species limited. A more extended search was then started to find such substances capable of inhibiting growth in transplantable mammalian carcinomata. Normal animal embryo skin and placenta yielded such extracts which inhibited transplantable mouse carcinomata but had no effect on transplantable mouse sarcomata^{120, 121}. It was necessary to use desiccated material to get the optimum effect, fresh tissues not proving very potent. In the more recent reports ether-soluble fractions of pre-lactating mammary gland had strong stimulating properties when tested against mouse cancers, and ether-insoluble fractions had strong inhibitors. The aqueous extract of this tissue had both stimulators and inhibitors which partially neutralized each other¹²². Morton and Beers¹²³ extracted material from fresh human connective tissue which had powerful inhibitors when tested against Rat Carcinoma No. 256. A most extensive and elaborate work on these substances has been produced by Maisin and his co-workers¹²⁴. They demonstrated that practically every organ contained both growth-inhibiting and growth-promoting factors. They also showed that most growth-promoting substances were water-soluble and relatively insoluble in ether, whereas the inhibiting substances were ether-soluble but for the most part insoluble in acetone. They used tarred animals as test objects and the growth substances were fed to them in their diets. They proved that these growth substances can pass the stomach and intestinal mucosa without being destroyed. This scattered selection from the literature will emphasize the relatively new aspects of the problem. There has been, as yet, only a preliminary scratching of the surface in this promising field of research. Much work of a chemical nature has been done in attempting to solve the riddle of malignancy. Voegtlin's¹²⁵ review of this phase of the subject should be consulted by every one interested in the cancer problem.

Theories to Explain the Fundamental Change—Many men have speculated upon the internal cellular change that is cancer. First of all, there are so many types of neoplastic growth that it is quite unlikely that cancer is a unit disease, having a common etiology. It is much more probable that the etiologic factors vary from organ to organ. The nature of the intimate cellular changes, however, transforming the normal cell into a malignant one,¹²⁶ may be the same whatever the tissue, organ or species. The older writers have stressed some phases of the cancer problem which still have an important place in the consideration of etiology. There is little doubt, for example, in the correctness of Cohnheim's theory that tumors may develop from masses of simple or complex tissue misplaced during embryonal development. These cells furnish the nidus of incompletely organized tissue upon which inciting factors may have a more rapid action. The dermoids, branchiogenic carcinomata, salivary gland tumors, the tumors

in the adrenal or remnants of the urogenital apparatus are striking examples McFarland, *et al*,¹²⁷ have offered support for a rational explanation on the origin of basal cell carcinomata founded on such a basis Billroth claimed that without previous changes in the originating tissue cancer did not exist This would account for the increased chances for malignancy supervening upon previously damaged tissues such as cancers in roentgen ray dermatitis, osteogenic sarcomas upon Paget's disease of bone, *etc* In fact, many of the carcinogenic hydrocarbons, tars, viruses, hormones, first prepare the tissues for the malignant change by disturbing their normal relationships—keratoses, papillary cysts, *etc* The chronic irritation theory and the loss of cell regulation—disorganization—still have a definite place in the etiology for some types of growth Even now Remmann¹²⁸ constantly stresses that the main difference between normal and cancerous tissues is the failure of the latter to completely differentiate and organize This was Hansemann's old plea, that the cells had lost their normal differentiation, specific function, and organization—a process which he called anaplasia The resulting cells failed to have their proper balancing factors so that they escaped from the restraining influence of the organization As a result, bizarre, irregular, asymmetric and multipolar mitoses could frequently be demonstrated in these lawless tissues The organizer tissues of Spemann may have a bearing on this problem At present this question is difficult to handle because most of our knowledge in testing for organizers is through the amphibians In these animals many tissues, even boiled or dead human material, will act as organizers

Many writers believe that the essential change must be a somatic mutation The faithful transmission of the malignant qualities of the cells from generation to generation, from animal to animal in transplantation, over many years indicates that the cells breed true This indicates surely that the tumor cells must differ genetically from those of the normal tissues from which they arose¹²⁹ But since also the sex cells are not involved in this process, it must be a somatic cell mutation¹³⁰ Boveri had a theory that cancer was a chromosomal aberration or a gene mutation This cannot be proved by genetical methods for cancer cells do not reproduce sexually It is only by sexual reproduction that nuclear changes can be distinguished from plasmatic ones Experimentally it has been possible to produce mutations by roentgen rays The experiments of the Furths and Butterworth,¹³¹ by which 15 times as many ovarian tumors, eight times as many cases of myelosis and seven times as many lymphosarcomata were caused in roentgen ray treated animals as in the controls are very suggestive

Lewis¹³² does not believe that there is any proof that chromosomal or gene alterations are responsible for malignant cells The chromosomes are numerous and small (48 in the human) and it will be a long time before they can be analyzed in any way comparable to that of the giant chromosomes of the salivary glands of the fruit fly He concludes that the chromosome or gene alterations have nothing to do with the origin of malignancy

There are amazing alterations in some of the chromosomes and the cytologic character of malignant cells does not seem to depend on the exact complement of chromosomes. The chromosomal alterations are symptoms and not the cause. Probably the change in malignancy is primarily a cytoplasmic one. Politzer¹³³ says that there are undoubted carcinoma cells of normal chromosome content. Polyploid, and other bizarre forms are frequent. But since abnormal forms can be found in tissues which are not malignant and since abnormality is not constant even in cancer tissue, this point cannot be used as a definite diagnostic factor. Ehrlich¹³⁴ says that all the known carcinogenic agents set up chromosomal disturbances. All cancers he examined had nuclei either twice or four times as large as those of the mother cell.

Mendelsohn¹³⁵ believed that he could tell when the onset of malignancy was about to occur in cysticercus cysts in the rat. He judged this by the presence of abnormal mitoses in the inflammatory reaction about the cysts. It was not noted in ordinary inflammatory reaction due to mustard. Drucker¹³⁶ thought that malignant transformation was an irreparable nuclear defect. Levine,¹³⁷ in beautiful study of the cytology of cancer, found many aberrations in the chromosome pattern but an astonishing degree of constancy and specificity in all the transplants. This was contrary to what one would expect from the exceedingly variable chromosome relations of the tumor cells. He concluded that there was no relation between polyploidy and the etiology of cancer. It has been shown that even when an animal tumor had been treated by sublethal doses of roentgen rays so that growth was checked and biopsies showed great abnormalities in many of the cells, on subsequent inoculation the tumor resumed its growth. The chromosome picture was no more abnormal than if it had not been rayed. Radiation did not produce a chromosomal mutation in this case. Warren¹³⁸ was able to differentiate carcinomata from sarcomata and lymphoblastomata by measuring the angles of the mitotic spindles in malignant cells.

The driving force resides within the cell but there is no evidence that the inciting agent is a part of the process once it has been initiated. Where it is possible to accurately measure the inciting agent it has not been found within the cell once malignancy has become well established. In an attempt to prove whether the cancer change arose from a chemical interaction between the carcinogenic hydrocarbons and the body cells, tests were made by the fluorescence spectrum. In this way as small quantities as 0.0004 mg could be detected.¹³⁹ After the fifth to sixth generation transplants of dibenzanthracene induced tumors, Lorenz and Shear¹⁴⁰ failed to find any evidence of the presence of this agent. Dibenzanthracene is distinctly fluorescent. It can easily be identified in microscopic sections with the aid of ultraviolet light. The tumors produced by it do not show any great retention of the compound.¹⁴¹

In metastases from osteogenic sarcomata produced by radium or mesothorium, there was no evidence of radioactivity.¹⁴² Even many of the

virus-induced tumors partake of this same quality. The investigators are unable to recover the virus from the malignant growths. The evolution of malignancy is a step by step process and not an immediate action.

The attempts to explain malignancy on the basis of a chemical change within the cell is a difficult one. If some such substance is formed it must be transmitted down to all the descendants. It must constantly renew itself in some manner. Murphy⁷¹ believes that some such substances are formed in chicken sarcomata. He likens them to the active principles extractable from the cells which can alter the types of the pneumococci. He calls them transmissible mutagens to distinguish them from viruses as he does not believe that the chicken sarcoma agents are alive.

Stanley's separation of a crystalline protein substance from the tobacco-mosaic virus disease¹⁴³, and the more recent separation of a similar crystalline from the Shope rabbit papilloma¹⁴⁴ may be the beginning of the explanation. These proteins apparently have the power to promote growth in tissues. They are extractable from the processes which they have produced.

The proponents of the virus theory of cancer growth must assume that viruses are present in many of the tissues of the body. These viruses remain dormant waiting for their opportunity to initiate the malignant change. They are protected by the cell wall from injury. This hypothesis cannot be refuted by experimentation for there is no way of proving or disproving it. The difficulties in handling the virus origin of cancer reside in the fact that it takes living cells to demonstrate the virus. Therefore, the experimentalist must constantly get his results with living cells. These are the important limiting factors. If the viruses are responsible for the unknown intracellular function of malignant tissue, it is difficult to understand why they do not enter other cells in the neighborhood and produce different type tumors. The cells of malignant tissues are constantly dying, which would release the effective agent. The supporters of the virus theory must maintain that the viruses can only act on a specific type of cell, or they must assume a multitude of different viruses, each one having a selective affinity for a different tissue. In one other respect the neoplastic viruses differ from other carcinogenic agents. Their action on tissues is not by a slow preparation but is relatively rapid. Metastases would require, as now, the transport of the original type cell which contained the virus, or else another type of tissue tumor would be expected from metastasis of the virus alone.

The fundamental cause of cancer is an intracellular alteration in the cells involved. This releases them from the regulation of the other cells. It makes them able to continue as independent cells. The ultimate causal agent at the same time releases them and makes them self-perpetuating. At the present we have no knowledge regarding the nature of this change. Theories advanced to explain it include the mutation theory, the virus theory, and intracellular chemical alterations. No one of these theories seem quite adequate to explain every type of tumor growth.

BIBLIOGRAPHY

- ¹ Pott, Percivall Cancer Scroti The Chirurgical Works of Percivall Pott, London Lowndes, 3, 225-229, 1783
- ² Haagensen, C D Occupational Neoplastic Disease Am Jour Cancer, 15, 641-703, 1931
- ³ Martland, H S The Occurrence of Malignancy in Radioactive Persons Am Jour Cancer, 15, 2435-2516, 1931
- ⁴ Pircham, A, and Sikl, H Cancer of the Lung in the Miners of Jachymov (Joachimsthal) Am Jour Cancer, 16, 681-722, 1932
- ⁵ Hoffman, W J Industrial and Occupational Cancer Preventive Med, 6, 7-34, 1936
- ⁶ Treves, N, and Pack, G T The Development of Cancer in Burn Scars Surg, Gynec, and Obstet, 51, 749-782, 1930
- ⁷ White, C, and Weidman, F D Pseudo-epitheliomatous Hyperplasia at the Margins of Cutaneous Ulcers J A M A, 88, 1959-1963, 1927
- ⁸ Knox, L C Epithelioma and the Chronic Varicose Ulcer J A M A, 85, 1046-1050, 1925
- ⁹ Roffo, A H Heliotrophism of Cholesterol in Relation to Skin Cancer Am Jour Cancer, 17, 42-57, 1933
- ¹⁰ Copeland, M M, and Martin, H E Xeroderma Pigmentosum Am Jour Cancer, 16, 1337-1357, 1932
- ¹¹ Franseen, C C, and Taylor, G W Arsenical Keratoses and Carcinomas Am Jour Cancer, 22, 287-307, 1934
- ¹² Strong, R P The Role Played by Helminths in the Production of Tumors in Man and Animals Internat Clin, 4, 68-92, 1931
- ¹³ Taylor, H C, Jr The Evidence for an Endocrine Factor in the Etiology of Mammary Tumors Am Jour Cancer, 27, 525-541, 1936
- ¹⁴ Ewing, J Modern Attitude Toward Traumatic Cancer Arch Path, 19, 690-728, 1935
- ¹⁵ Clunet, J Recherches experimentales sur les tumeurs malignes, Paris, 1910
- ¹⁶ Fibiger, J Untersuchungen über eine Nematode (Spiroptera sp n) und deren Fähigkeit, papillomatose und carcinomatose Geschwulstbildungen im Magen der Ratte hervorzurufen Ztschr f Krebsforsch, 13, 217-280, 1913
- ¹⁷ Yamagiwa, K, and Ichikawa, K Experimentelle Studie über die Pathogenese der Epithelialgeschwulste Mitt d med Gesellsch zu Tokyo, 15, 295, 1916
- ¹⁸ Leitch, A Gallstones and Cancer of the Gall-bladder Brit Med Jour, 2, 451-454, 1924
- ¹⁹ Adair, F E, and Bagg, H J Breast Stasis as the Cause of Mammary Cancer Internat Clin, 4, 19-26, 1925
- ²⁰ Berenblum, I Tumor Formation Following Freezing with Carbon Dioxide Snow Brit Jour Exper Path, 10, 179-184, 1929, Further Investigations of the Induction of Tumors with Carbon Dioxide Snow Brit Jour Exper Path, 11, 208-211, 1930
- ²¹ Mansens, B J Huidkanker bij muizen door Koolzuursneeuw Nederl tijdschr v geneesk, 75, 1444, 1931
- ²² Roffo, A H Production of Carcinoma and Sarcoma in Rats by Exposure to Sunlight Bol Inst de med exper para el estudio trat del cancer, 10, 417, 1933
- ²³ Findlay, G M Ultra-violet Light and Skin Cancer Lancet, 2, 1070-1073, 1928, Cutaneous Papillomata in the Rat Following Exposure to Ultra-violet Light Lancet, 1, 1229-1231, 1930
- ²⁴ Putschar, W, and Holtz, F Erzeugung von Hautkrebsen bei Ratten durch Langdauernde Ultraviolettbestrahlung Ztschr f Krebsforsch, 33, 219-260, 1930
- ²⁵ Herlitz, C W, Jundell, I, and Wahlgren, F Durch Ultraviolettbestrahlung erzeugte Maligne Neubildungen bei Weissen Mäusen Acta Pediat, 10, 321-352, 1931

- ²⁰ Daels, F Experimentelle bosartige Geschwulste Arch f klin Chir, 177, 144-145, 1933
- ²¹ Biltris, R Tumeurs malignes observees chez le cobaye apres introduction de sources radio-actives Bull assoc franç p l'etude du cancer, 22, 438-468, 1933
- ²² Petrov, N, and Krotkina, N Experimentelles Gallenblasen- und Lebercarcinom Ztschr f Krebsforsch, 38, 249-263, 1933
- ²³ Lacassagne, A Tumeurs malignes provoques chez le lapin par l'irradiation de foyers inflammatoires Compt rend Acad d Sc, 196, 69-71, 1933
- ²⁴ Ludin, M Knochensarkom nach experimenteller Roentgenbestrahlung Acta Radiol, 15, 553-556, 1934
- ²⁵ Schurch, O, and Uehlinger, E Experimentelles Knochensarkom nach Radiumbestrahlung bei einem Kaninchen Ztschr f Krebsforsch, 33, 476-484, 1931, Experimentelle Erzeugung von Knochensarkom durch Radium beim Kaninchen Schweiz med Wchnschr, 15, 664-667, 1934
- ²⁶ Sabin, F R, Doan, C A, and Forkner, C E The Production of Osteogenic Sarcomata and the Effects on Lymph Nodes and Bone Marrow of Intravenous Injections of Radium Chloride and Mesothorium in Rabbits Jour Exper Med, 56, 267-289, 1932
- ²⁷ Bullock, F D, and Curtis, M R The Experimental Production of Sarcoma of the Liver of Rats Proc N Y Path Soc, 20, 149, 1920, A Study of the Reactions of the Tissues of the Rat's Liver to the Larvae of *Tema Crassicolis* and the Histogenesis of Cysticercus Sarcoma J Cancer Research, 8, 446-481, 1924
- ²⁸ Kennaway, E L Experiments on Cancer-producing Substances Brit Med Jour, 2, 1-4, 1925
- ²⁹ Spielmann, P E The Constituents of Coal Tar London, Longmans, Green & Co, 1924
- ³⁰ Kennaway, E L, and Hieger, I Carcinogenic Substances and Their Fluorescence Spectra Brit Med Jour, 1, 1044-1046, 1930
- ³¹ Kennaway, E L Further Experiments on Cancer-producing Substances Biochem Jour, 24, 497-504, 1930
- ³² Hieger, I The Spectra of Cancer producing Tars and Oils and of Related Substances Biochem Jour, 24, 505-511, 1930
- ³³ Clar, E Zur Kenntniss mehrkernigen aromatischen Kohlenwasserstoffe und ihrer Abkommlinge I Mitt Dibenzanthracen und ihre Chinone Ber d deutsch chem Gesellsch, 62 B, 350-359, 1929
- ³⁴ Cook, J W, Hieger, I, Kennaway, E L, and Mayneord, W V The Production of Cancer by Pure Hydrocarbons Proc Roy Soc London, Ser B 111, 455-484, 1932
- ³⁵ Burrows, H, Hieger, I, and Kennaway, E L The Experimental Production of Tumors of Connective Tissue Am Jour Cancer, 16, 57-67, 1932
- ³⁶ Cook, J W, Hewett, C L, and Hieger, I Isolation of a Cancer-producing Hydrocarbon from Coal Tar, Parts I, II, III Jour Chem Soc, 144, 395-405, 1933
- ³⁷ Cook, J W, Haslewood, G A D, Hewett, C L, Hieger, I, Kennaway, E L, and Mayneord, W V Chemical Compounds as Carcinogenic Agents Am Jour Cancer, 29, 219-259, 1937
- ³⁸ Cook, J W Discussion on the Experimental Production of Malignant Tumors Proc Roy Soc London, Ser B, 113, 273-277, 1933
- ³⁹ Morton, A A, Branch, C F, and Clapp, D B Production of Cancer by Hydrocarbons Other than Those of Phenanthrene Type Am Jour Cancer, 26, 754-760, 1936
- ⁴⁰ Sasaki, F, and Yoshida, T Experimentelle Erzeugung des Lebercarcinoms durch Futterung mit o-Amidoazotoluol Virchows Arch f path Anat, 295, 175-200, 1935

- ⁴⁷ Browning, C H, Cohen, J B, Cooper, K E, Ellingworth, S, and Gulbransen, R The Antiseptic and Trypanocidal Action of Some Benzoalamino Quinoline and Styryl Compounds *Proc Roy Soc, Ser B*, 113, 300-307, 1933
- ⁴⁸ Fieser, L F, Fieser, M, Hershberg, E B, Newman, M S, Seligman A M, and Shear, M J Carcinogenic Activity of the Cholanthrenes and of Other 1 2-Benzanthracene Derivatives *Am Jour Cancer*, 29, 260-268, 1937
- ⁴⁹ Loeb, Leo Quantitative Relations Between Factors Causing Cancer and Rapidity and Frequency of Resulting Cancerous Transformation *Jour Cancer Res*, 8, 274-284, 1924
- ⁵⁰ Lacassagne, A Hormonal Pathogenesis of Adenocarcinoma of the Breast *Am Jour Cancer*, 27, 217-228, 1936
- ⁵¹ Gardner, W U, Smith, G M, Allen, E, and Strong, L C Cancer of the Mammary Glands Induced in Male Mice Receiving Estrogenic Hormone *Arch Path*, 21, 265-272, 1936
- ⁵² Burrows, H, and Kennaway, N M On Some Effects Produced by Applying Oestrin to the Skin of Mice *Am Jour Cancer*, 20, 48-57, 1934
- ⁵³ Lacassagne, A Comparative Study of the Carcinogenic Actions of Certain Oestrogenic Hormones *Am Jour Cancer*, 28, 735-740, 1936
- ⁵⁴ Cook, J W, and Dodds, E C Sex Hormones and Cancer-producing Compounds *nature*, 131, 205-206, 1933
- ⁵⁵ Loeb, Leo Estrogenic Hormones and Carcinogenesis *J A M A*, 104, 1597-1601, 1935
- ⁵⁶ Michalowsky, I Eine experimentelle Erzeugung teratoider Geschwulste der Hoden beim Hahn *Virchows Arch f path Anat*, 267, 27-62, 1928
- ⁵⁷ Bagg, H J Experimental Production of Teratoma Testis in the Fowl *Am Jour Cancer*, 26, 69-84, 1936
- ⁵⁸ Ferguson, R S Quantitative Behavior of Prolan A in Teratoma Testis *Am Jour Cancer*, 18, 269-295, 1933
- ⁵⁹ Zondek, H, Zondek, B, and Hartoch, W Prolan und Tumorwachstum *Klin Wehnschr*, 11, 1785-1786, 1932
- ⁶⁰ Duran-Reynals, F The Effect of Testicle Extract and of Normal Serum on a Transplantable Epithelial Tumor of the Rabbit *Jour Exper Med*, 54, 493-498, 1931
- ⁶¹ Jaffe, H L, Bodansky, A, and Blair, J E The Effects of Parathormone and Ammonium Chloride on the Bones of Rabbits *Jour Exper Med*, 55, 695-701, 1932
- ⁶² Johnson, J L, and Wilder, R M Experimental Chronic Hyperparathyroidism *Am Jour Med Sci*, 182, 800-807, 1931
- ⁶³ Adamstone, F B A Lymphoblastoma Occurring in Young Chicks Reared on a Diet Treated with Ferric Chloride to Destroy Vitamin E *Am Jour Cancer*, 28, 540-549, 1936
- ⁶⁴ Rowntree, L G, Lansbury, J, and Steinberg, A Neoplasms in Albino Rats Resulting from the Feeding of Crude Wheat Germ Oil Made by Ether Extraction *Proc Soc Exper Biol and Med*, 36, 424-426, 1937
- ⁶⁵ Dorrance, G M, and Ciecone, E F Production of Sarcoma in Albino Rats as a Result of Feeding Crude Wheat Germ Oil *Proc Soc Exper Biol and Med*, 36, 426-427, 1937
- ⁶⁶ Watson, A F, and Mellanby, E Tar Cancer in Mice II The Condition of the Skin When Modified by External Treatment or Diet, as a Factor in Influencing the Cancerous Reaction *Brit Jour Exper Path*, 11, 311-322, 1930
- ⁶⁷ Bittner, J J Differences Observed in the Tumor Incidence of an Albino Strain of Mice Following a Change in Diet *Am Jour Cancer*, 25, 791-796, 1935
- ⁶⁸ Rous, P A Sarcoma of the Fowl Transmissible by an Agent Separable from the Tumor Cells *Jour Exper Med*, 13, 397-411, 1911
- ⁶⁹ Murphy, J B Transmission by Desiccate *Jour Exper Med*, 13, footnote 399, 1911

- ⁷⁰ Ellermann, V Experimentelle Leukämie bei Hühnern Verhandl deutsch path Gesellsch, 12, 224, 1908
- ⁷¹ Claude, A, and Murphy, J B Transmissible Tumors of the Fowl Physiol Rev, 13, 246-275, 1933
- ⁷² Rivers, T M The Nature of Viruses Physiol Rev, 12, 423-452, 1932
- ⁷³ Shope, R E Infectious Papillomatosis of Rabbits J Exper Med, 58, 607-624, 1933
- ⁷⁴ Shope, R E A Transmissible Tumor-like Condition in Rabbits Jour Exper Med, 56, 793-802, 1932
- ⁷⁵ Rous, P, and Beard, J W A Virus-induced Mammalian Growth with the Characteristics of a Tumor Jour Exper Med, 60, 701-722, 741-766, 1934
- ⁷⁶ Rous, P, and Kidd, J G Carcinogenic Effect of a Virus upon Tarred Skin Science, 83, 468-469, 1936
- ⁷⁷ Berry, G P, and Dedrick, H M A Method for Changing the Virus of Rabbit Fibroma (Shope) into that of Infectious Myxomatosis (Sanarelli) Jour Bacteriol, 31, 50-51, 1936
- ⁷⁸ Lucke, B A Neoplastic Disease of the Kidney of the Frog Am Jour Cancer, 20, 324-379, 1934
- ⁷⁹ Oberling, C, and Guérin, M Lésions tumorales en rapport avec la leucémie transmissible des poules Bull Assoc franç p l'étude du Cancer, 22, 180-214, 1933
- ⁸⁰ Meyer, A R, and Engelbreth-Holm, J Experimentelle Studien über die Beziehungen Zwischen Hühnerleukose und Sarkom an der Hand eines Stammes von über tagbarer Leukose-Sarkom-Kombination Acta Path et Microbiol Scandinav, 10, 380-428, 1933
- ⁸¹ Furth, J Lymphomatosis, Myelomatosis and Endothelioma of Chickens Caused by a Filterable Agent Jour Exper Med, 58, 253-275, 1933
- ⁸² Troisier, J Leucose et sarcomatose des poules unite de virus Ann Inst Pasteur, 55, 501-517, 1935
- ⁸³ McIntosh, J On the Nature of the Tumors Induced in Fowls by Injections of Tar Brit Jour Exper Path, 14, 422-434, 1933
- ⁸⁴ Peacock, P R Studies of Fowl Tumors Induced by Carcinogenic Agents II Attempted Transmission by Cell free Material Am Jour Cancer, 25, 49-65, 1935
- ⁸⁵ Murphy, J B, and Landsteiner, K Experimental Production and Transmission of Tar Sarcomas in Chickens Jour Exper Med, 41, 807-816, 1925
- ⁸⁶ Sturm, E, and Murphy, J B Further Observations on Experimentally Produced Sarcoma of Chicken Jour Exper Med, 47, 493-502, 1928
- ⁸⁷ Murphy, J B, Helmer, O H, Claude, A, and Sturm, E Observations Concerning the Causative Agent of a Chicken Tumor Science, 73, 266, 1931
- ⁸⁸ Lewis, M R The Production of Tumors by Means of Purified (Protein Removed) Tumor Extracts Am Jour Cancer, 15, 2248-2251, 1931
- ⁸⁹ Andrewes, C H Evidence for the Presence of Virus in a Non-filterable Tar Sarcoma of the Fowl Jour Path and Bact, 43, 23-33, 1936
- ⁹⁰ Parsons, L D Sarcoma Produced by Cell-free Filtrates of Mal Sarcoma I Jour Path and Bact, 43, 1-22, 1936
- ⁹¹ Andrewes, C H Viruses in Relation to Aetiology of Tumors Lancet, 2, 63-69, 117-123, 1934
- ⁹² Rous, P The Virus Tumors and the Tumor Problem Am Jour Cancer, 28, 233-271, 1936
- ⁹³ DeMonbreun, W A, and Goodpasture, E W An Experimental Investigation Concerning the Nature of Contagious Lymphosarcoma of Dogs Am Jour Cancer, 21, 295-321, 1934
- ⁹⁴ Curtis, M R, Dunning, W F, and Bullock, F D Genetic Factors in Relation to the Etiology of Malignant Tumors Am Jour Cancer, 17, 894-923, 1933, Further Evidence in Support of the Somatic Mutation Hypothesis of the Origin of Cancer Am Jour Cancer, 21, 86-98, 1934, Duration and Extent of Irritation Versus

- Genetic Constitution in the Etiology of Malignant Tumors Am Jour Cancer, 21, 554-570, 1934
- ⁹⁶ Leitch, A The Effect of Cessation of the Irritant on the Development of Experimental Tar Cancer Brit Med Jour, 2, 1101-1103, 1922
- ⁹⁷ Dobrovolskaia-Zavadskaja, N Heredity of Cancer Am Jour Cancer, 18, 357-379, 1933
- ⁹⁸ Wells, H G The Nature and Etiology of Cancer Am Jour Cancer, 15, 1919-1963, 1931
- ⁹⁹ Blacker, C P The Chances of Morbid Inheritance Baltimore, Wm Wood & Co., 1934
- ¹⁰⁰ McFarland, J, and Meade, T S The Genetic Origin of Tumors Supported by Their Simultaneous and Symmetrical Occurrence in Homologous Twins Am Jour Med Sci, 184, 66-80, 1932
- ¹⁰¹ Miltzer, R E Carcinoma of the Stomach in Identical Twins Am Jour Cancer, 25, 544-545, 1935
- ¹⁰² Tyzzer, E E A Study of Inheritance in Mice with Reference to Their Susceptibility to Transplantable Tumors Jour Med Res, 21, 519-547, 1909
- ¹⁰³ Murray, J A Fourth Scientific Report on the Investigations of the Imperial Cancer Research Fund London, Taylor and Francis, 1911, p 114
- ¹⁰⁴ Lathrop, A E C, and Loch, Leo Further Investigations on the Origin of Tumors in Mice Jour Cancer Research, 4, 137-179, 1919
- ¹⁰⁵ Slye, Maude The Fundamental Harmonies and the Fundamental Differences Between Spontaneous Neoplasms and All Experimentally Produced Tumors Jour Cancer Research, 8, 240-273, 1924
- ¹⁰⁶ Little, C C The Present Status of Our Knowledge of Heredity and Cancer J A M A, 106, 2234-2235, 1936
- ¹⁰⁷ The Staff of the Roscoe B Jackson Mem Lab The Constitutional Factor in the Incidence of Mammary Tumors Am Jour Cancer, 27, 551-555, 1936
- ¹⁰⁸ Murray, W S Ovarian Secretion and Tumor Incidence Jour Cancer Research, 12, 18-25, 1928
- ¹⁰⁹ Fekete, E, and Green, C V The Influence of Complete Blockage of the Nipple on the Incidence and Location of Spontaneous Mammary Tumors in Mice Am Jour Cancer, 27, 513-515, 1936
- ¹¹⁰ Bagg, H J Further Studies on the Relation of Functional Activity to Mammary Carcinoma in Mice Am Jour Cancer, 27, 542-550, 1936
- ¹¹¹ MacDowell, E C Genetic Aspects of Mouse Leukemia Am Jour Cancer, 26, 85-101, 1936
- ¹¹² Lynch, C J Susceptibility of Mouse Strains to Lung Tumor and Sarcoma Induced by 1, 2, 5, 6-Dibenzanthracene Proc Soc Exper Biol and Med, 33, 401-403, 1935
- ¹¹³ Dunning, W F, Curtis, M R, and Bullock, F D Respective Roles of Heredity and Somatic Mutation in the Origin of Malignancy Am Jour Cancer, 28, 681-712, 1936
- ¹¹⁴ Stark, M B An Hereditary Tumor in the Fruit Fly, Drosophila Jour Cancer Res, 3, 279-301, 1918
- ¹¹⁵ Stark, M B Development of Certain Hereditary Tumors in Drosophila Melanogaster Hahnemann Monthly, 68, 674-675, 1933
- ¹¹⁶ Gordon, M Hereditary Basis of Melanosis in Hybrid Fishes Am Jour Cancer, 15, 1495-1523, 1931
- ¹¹⁷ Macklin, M T Heredity in Cancer and Its Value as an Aid in Early Diagnosis Edinburgh Med Jour, 42, 49-67, 1935
- ¹¹⁸ Warburg, O Metabolism of Carcinoma Cells Jour Cancer Res, 9, 148-163, 1925
- ¹¹⁹ Murphy, J B, Helmar, O M, Claude, A, and Sturm, E Observations Concerning the Causative Agent of a Chicken Tumor Science, 73, 266-268, 1931

- ¹¹⁰ Murphy, J B, and Sturm, E Properties of Causative Agent of Chicken Tumor, Action of Associated Inhibitor on Mouse Tumors Jour Exper Med, 56, 483-492, 1932
- ¹²⁰ Murphy, J B, and Sturm, E A Factor from Normal Tissues Inhibiting Tumor Growth Jour Exper Med, 60, 293-303, 1934
- ¹²¹ Murphy, J B, and Sturm, E The Effect of a Growth-retarding Factor from Normal Tissues on Spontaneous Cancer of Mice Jour Exper Med, 60, 305-315, 1934
- ¹²² Murphy, J B Inhibition of Malignant Growth by a Factor from Normal Tissue Reports of Internat Congress of Science and Social Campaign Against Cancer, 1936
- ¹²³ Morton, J J, and Beers, D N The Demonstration of a Tumor Growth-inhibiting Factor from Normal Human Connective Tissue Jour Exper Med, 61, 59-66, 1935
- ¹²⁴ Maisin, J, and Pourbaix, Y Growth-Promoting and Growth-inhibiting Substance Extracted from Normal Organs An Experimental Study of Diet in Tar Cancer Am Jour Cancer, 24, 357-386, 1935
- ¹²⁵ Voegtlin, C Biochemistry of Malignant Tissues Physiol Rev, 17, 92-118, 1937
- ¹²⁶ Cramer, W The Importance of Statistical Investigations in the Campaign Against Cancer Am Jour Cancer, 29, 1-19, 1937
- ¹²⁷ McFarland, J, Ciccone, E F, and Gelehrter, J On the Dysontogenetic Origin of Basal-cell Carcinoma Am Jour Cancer, 25, 273-281, 1935
- ¹²⁸ Reimann, S P Studies of Cell Potencies and Some Relations to Neoplasia Ann Int Med, 8, 504-508, 1934
- ¹²⁹ Murray, J A, *et al* Discussion on Experimental Production of Malignant Tumors Proc Roy Soc London, Ser B, 113, 268-292, 1933
- ¹³⁰ Little, C C The Bearing of Genetic Work with Transplantable Tumors on the Genetics of Spontaneous Tumors in Mice Am Jour Cancer, 22, 578-585, 1934
- ¹³¹ Furth, J, and Furth, O Neoplastic Disease Produced in Mice by General Irradiation with X-rays Am Jour Cancer, 28, 54-65, 1936
- ¹³² Furth, J, and Butterworth, J S Am Jour Cancer, 28, 66-95, 1936
- ¹³² Lewis, W H Normal and Malignant Cells Science, 81, 545-553, 1935
- ¹³³ Politzer, G Die Zellteilung im Karzinom Wien klin Wchnschr, 48, 1055-1057, 1935
- ¹³⁴ Ehrlich, W E Nuclear Sizes in Growth Disturbances with Special Reference to the Tumor Cell Nucleus Am Jour Med Sci, 192, 772-790, 1935
- ¹³⁵ Mendelsohn, W The Significance of Abnormal Mitoses in Malignancy Am Jour Cancer, 24, 626-636, 1935
- ¹³⁶ Druckrey, H Untersuchungen und Bemerkungen zur Krebsfrage Klin Wchnschr, 15, 401-404, 433-436, 1936
- ¹³⁷ Levine, M Studies in the Cytology of Cancer Am Jour Cancer, 15, 788-834, 1411-1494, 1931
- ¹³⁸ Warren, S Angle of Mitotic Spindles in Malignant Cells Am Jour Path, 9, 781-788, 1933
- ¹³⁹ Hieger, I On the Mechanism of Carcinogenesis by Chemical Compounds Am Jour Cancer, 28, 522-529, 1936
- ¹⁴⁰ Lorenz, E, and Shear, M J The Detection of Dibenzanthracene in Mouse Tumors Induced by this Hydrocarbon Am Jour Cancer, 26, 333-343, 1936
- ¹⁴¹ Branch, C F Dibenzanthracene Tumors in Controlled Strains of Mice Am Jour Cancer, 26, 110-114, 1936
- ¹⁴² Schurch, O, and Uehlinger, E Uber experimentelle Knochentumoren Arch f klin Chir, 183, 704-719, 1935
- ¹⁴³ Stanley, W M Isolation of a Crystalline Protein Possessing the Properties of Tobacco-mosaic Virus Science, 81, 644, 1935
- ¹⁴⁴ Beard, J W, and Wyckoff, R W G The Isolation of a Homogeneous Heavy Protein from Virus-induced Rabbit Papillomas Science, 85, 201-202, 1937

DISCUSSION —THE PRESIDENT, DR EVARTS A GRAHAM (St Louis)
It seems to me that one of the most dramatic discoveries in medicine is the relationship, to which Doctor Morton alluded, of apparently normal hormonal secretion to the development of cancer

The brilliant experiments of Lacassaigne, a colleague of Professor Coutard, in this subject are among the most dramatic discoveries of medicine that have been made in all time. Yet they have not achieved the prominence which they should have. The fact, for example, that presumably normal ovarian hormone can produce cancer of the breast not only in the female subject but in the male subject, and produce cancer of the breast in a very large percentage of experimental animals in which it is used, is a contribution which seems to me to be of the very first magnitude.

I am sure that many of us in this audience have seen striking confirmations of this fact. In St Louis, for example, we have had several patients, young women, with extensive inoperable carcinoma of the breast, fixation to the chest wall, axillary and cervical node involvement, metastases to the spine and elsewhere, who have been brought into the hospital on stretchers because they were unable to use their legs or their arms, sometimes totally paralyzed on account of extensive metastases. At the suggestion of Doctor Copher, some of these patients have been given a course of roentgenotherapy of the ovaries, merely to prevent the secretion of the ovarian hormones, and most amazing results have occurred. After about a year some of these patients have been able to return, happy, with the paralysis gone, doing their housework, and with astonishing regression of both the breast tumor itself and the metastases. In my opinion, such a result once seen in one patient is so dramatic that it makes this discovery of the hormonal relationship to cancer as startling as anything I know of in the history of medicine. Yet of course there are many unsolved problems, as Doctor Morton indicated.

So far as I know, no one has the least conception at the present time, for example, of why carcinoma of the breast is not a bilateral disease instead of practically always a unilateral disease, if it is a simple relationship of hormonal secretion, for instance, to the cells in the breast tissue. That constitutes a problem which still remains unsolved.

MALIGNANT CHANGES IN THE FORESTOMACH OF RATS* RELATED TO LOW PROTEIN (CASEIN) DIET AND PREVENTED WITH CYSTINE

GEORGE R. SHARPLESS, Sc D

DETROIT, MICH

FROM THE DEPARTMENT OF LABORATORIES OF THE HENRY FORD HOSPITAL, DETROIT, MICH

EXTENSIVE morphologic changes have been observed in the forestomach mucosa of rats fed purified diets. These diets were qualitatively complete but quantitatively deficient in protein. Because an explanation of their cause might contribute to the knowledge of proliferative lesions in general, an attempt was made to determine the etiology of the lesions.

A brief resume of previous investigations concerning these lesions will indicate the confusion that exists regarding their etiology. Fibiger¹ produced gastric carcinoma in rats by continuously infecting them with *Spiroptera*. Recent studies have shown that the diet used by Fibiger will produce precancerous changes which are made more severe by *Spiroptera*. Pappenheimer and Larimore² first demonstrated that the lesions were related to a deficiency in the diet. They did not find the nature of the deficiency, but they did find that neither cod liver oil nor vitamin B₁ protected against the lesions. Fujimaki³ produced the lesions by feeding a vitamin A deficient diet. His observations have been cited as another instance of the pathology of vitamin A deficiency. However, he later found that vitamin A did not prevent the lesions. Wolbach and Howe,⁴ in their study of the pathologic changes accompanying avitaminosis A, found that, other than atrophy of the mucosa of the stomach, no changes occurred.

A number of reports suggest that vitamin B deficiency may be the cause of the lesions. In a number of these studies a protein or cystine deficiency is not present. Howes and Vivier⁵ have reviewed and discussed the relation of vitamin B to production of the lesions. A possible relation between these findings and those reported here is presented in the discussion.

The diet used to produce the lesions is as follows:

Casein (vitamin free)	4.0%
Dried yeast	5.0%
Salts, No. 185 (McCollum)	4.0%
Butterfat	5.0%
Carbohydrate (corn starch, sucrose, or dextrin)	82.0%
Vioosterol, 15 drops per kilo	0.7% approximately

* The appended remarks were presented by Dr. Roy D. McClure (Detroit, Mich.) in discussion of the paper by Dr. John J. Morton (Rochester, N. Y.) on the "Etiology of Cancer in the Light of Our Present Knowledge," read before the American Surgical Association at New York, June 4, 1937. A more detailed and complete consideration of the subject, of which this is merely a summary, will appear shortly in *The American Journal of Cancer*.

Qualitatively this diet provides all of the essentials for growth and reproduction in the rat. However, it is quantitatively deficient in protein, which in turn is deficient in cystine.

The lesions which will be described are caused by the protein deficiency. When the casein content is raised to 12.0 per cent, no changes occur in the stomach. When 0.2 per cent cystine is added to the above diet the lesions do not occur. In order to give the physical properties of a normal protein content and keep the cystine low, 10 per cent gelatine has been added to the diet. The lesions appeared in these animals similar to their litter-mate controls. Variations in the vitamin additions and the type of carbohydrate made little difference in the development of the lesions.



FIG. 1.—The normal stomach shown on the left. The early type of lesion in the forestomach is shown on the right. Almost the entire area is hyperplastic and a few ulcerations can be seen.

Young male and female rats have been used in all of the experiments. All rats (125) which have been fed the above diet for three months or more have shown the lesions—some more advanced than others. Over 200 animals fed the stock diet have been examined and no changes were seen in the stomachs of any of them.

The normal rat's stomach is divided into two portions, a forestomach, sometimes called the rumen, and the glandular portion. Normally the forestomach is sharply divided from the glandular portion by a smooth, elevated linear ridge which passes to either side of the cardiac orifice of the esophagus. Elsewhere the internal surface is uniformly smooth. Histologically the forestomach, including the limiting ridge, is lined with squamous epithelium, surmounted by a thin keratin layer. The thickness of this epithelial layer varies with the state of distention of the stomach.

When the organ is contracted, the mucosa is thrown up into regular corrugations

The lesions occur only in the forestomach. The gross appearance of the lesion varies from a few small elevated round or oval disks to long ridges of thickened epithelium with small papillomatous projections. There is a depression in the center of the ridges and disks which may show ulceration. In animals with a severe type of lesion the epithelium becomes so greatly thickened that its elasticity has been lost. In these cases, the papillomatous growths nearly occlude the lumen of the forestomach.

Older lesions very often show epithelial cysts in the wall of the forestomach. Although they may occur in any or all parts of the forestomach, the lesions are found most frequently near the limiting ridges and in particular near the orifice of the esophagus (Fig 1)



FIG 2—Medium power magnification of normal forestomach showing the normal epithelium in the contracted organ with the muscularis mucosa, submucosa, and muscularis



FIG 3—Medium power magnification showing numerous masses of squamous epithelium below the papillae. The epithelium is very active in these areas

Microscopic Appearance—The epithelium in the normal animal rests almost directly upon the well developed muscularis mucosa from which it is separated by a delicate connective tissue. This zone is very inconspicuous in the normal organ except at the limiting ridge where the elevated epithelium is supported by a considerable amount of rather dense muscular and connective tissue. Between the muscularis mucosa and the muscularis there is a well defined layer of very loose areolar connective tissue which permits the epithelium to adapt itself to varying states of distention or contraction (Fig 2)

The early lesion is characterized by a greatly thickened squamous epithelium. The thickening is accompanied by considerable papilloma formation at the surface and hypertrophy of the papillae at the base (Fig 4). The hypertrophied papillae frequently cause thinning of the muscularis mucosa. In many cases, the continuity of the muscularis appears to be broken and a spur of epithelium extends into the submucosa. The spurs proliferate and keratinize, giving rise to the epithelial cysts which are common in animals which have been fed the diet six months or more.

Numerous small masses of active squamous epithelium are often seen between the hypertrophied papillae and the muscularis mucosa (Fig 3). The



FIG 4.—Low power magnification of the early type lesion showing increased thickness of the epithelium with papilloma formation at the surface and hypertrophy of the papillae at the base.

epithelium is very active in these areas and as many as 18 mitotic figures have been seen in one field under high magnification.

Ulceration of the epithelium may occur (Fig 5). The ulcer is usually superficial but sometimes it extends into the submucosa.

In old lesions, the epithelium may invade the muscularis mucosa (Fig 6) or may invade the submucosa and muscularis (Fig 7).

Metastases of this lesion have never been found. Two rats had carcinoma which was primary in the lung and did metastasize, but its relation to the diet is not clear since it was found in only two cases. There have been no spontaneous malignant tumors in the stock colony during the last four years. The occurrence of carcinoma in rats fed a cystine deficient diet is of interest since it has been recently reported that inhibition of growth of transplanted tumors occurs in rats fed similar diets.

Other areas of squamous epithelium are neither thickened nor hyperactive; the pelvis of the kidney, urinary bladder, and tongue have been examined.

It has been shown by Itter, Orant, and McCollum that sulphur metabolism



FIG 5—Low power magnification showing ulceration of hypertrophied epithelium and the edge of an epithelial cyst

FIG 6—Low power magnification showing greatly thickened epithelium with active proliferation and invasion of the muscularis mucosa by the epithelium

FIG 7—Low power magnification showing active invasion of the muscularis by the epithelium with numerous epithelial pearls throughout. There is no muscularis mucosa visible and the submucosa is not definite

is faulty in vitamin B₂ deficiency. It is also reported that patients with pellagra have somewhat similar lesions in the epithelium of the lower end of the esophagus together with a subnormal concentration of cystine in their fingernails. These facts suggest that some factor of the vitamin B complex is necessary for normal sulphur metabolism. The reports in the literature which show that lesions similar to those describe above are produced under certain conditions by vitamin B deficiency may therefore be correlated with the above findings.

SUMMARY

(1) Hyperplasia of the forestomach epithelium is produced in 100 per cent of rats fed a low protein (casein) diet.

(2) Older lesions sometimes show the active epithelium invading the muscularis mucosa and more rarely the submucosa and muscularis.

(3) The hyperplasia is prevented by feeding cystine with the diet.

(4) The vitamins are not related to the changes but under different experimental conditions a deficiency of some part of the vitamin B complex may induce similar changes.

REFERENCES

- ¹ Fibiger, Johannes. Untersuchungen über eine Nematode (Spiroptera) und deren Fähigkeit, papillomatose und carcinomatose Geschwulstbildungen im Magen der Ratte hervorzurufen. *Ztschr f Krebsforsch*, 13, 213, 1913.
- ² Pappenheimer, Alwin M., and Larimore, Louise D. The Occurrence of Gastric Lesions in Rats. Their Relation to Dietary Deficiency and Hair Ingestion. *J Exper Med*, 40, 719, 1924.
- ³ Fujimaki, Yoshitomo. Formation of Gastric Carcinoma in Albino Rats Fed on Deficient Diets. *J Cancer Res*, 10, 469, 1926.
- ⁴ Wolbach, W. Burt, and Howe, Percy R. Tissue Changes Following Deprivation of Fat Soluble A Vitamin. *J Exper Med*, 42, 753, 1925.
- ⁵ Howes, Edward L., and Vivier, Peter J. The Relation of Diet to the Occurrence of Gastric Lesions in the Rat. *Am J Path*, 12, 689, 1936.

OUR RESPONSIBILITY TOWARD ORAL CANCER

VILRAY P BLAIR, M D , JAMES BARRETT BROWN, M D , AND
LOUIS T BYARS, M D

ST LOUIS, MO

CANCER within the mouth can, from its earliest appearance, usually be verified by clinical observation and, rather soon after treatment, failure or success of local control can be determined with fair accuracy. On the contrary, early metastases in the neck are difficult to determine even with biopsy, and nothing but the passage of time will disprove their presence. The growth of squamous cell cancer within a neck node two, four, six or eight years after the cure of an ulcer on the lip or tongue has often been observed. This, of itself, makes it quite difficult to establish any satisfactory statistical comparison between the results obtainable by radiation and by a block excision in the treatment of the cervical nodes.

Before the discovery of radiation therapy, growths of the mouth and lower lip were treated by local excision followed by or combined with a block lymphatic node dissection. During the past ten years, with increasing confidence, we have changed over to the use of radon in gold seeds for the treatment of most intra-oral and pharyngeal lesions, combined with block dissection of the neck where primary healing of the local lesion has been obtained. Because of their apparent high resistance to radiation, and because of the extreme pain following over-radiation of bone, those growths arising in the mucous lining of the cheek or the covering of the jaw bone are still treated by a combination of cautery excision or destruction, and an upper neck dissection in one stage.

From our own reasoning and observation and from published statistics, we have not found any sufficient reason for abandoning the plan of complete or partial block excision of the imperiled lymphatic areas whenever practicable. Since the general introduction of radium, we have seen too few early lip cases to be of any comparative value.

In our own patients, treated before 1930,¹ in the two stage procedure there was a 49 per cent mortality, and all deaths occurred in patients in whom the nodes were so widely fixed that at the present time these would be considered inoperable, not only because of the high death rate, but in addition, none of those who survived operation were found to be alive five years afterward. In 48 patients without fixation of the nodes there were no post-operative deaths. In another series of patients in which the growths were so far advanced that one stage operations were performed, the mortality rate mounted to 34 per cent. These two series, before 1930, give a 20 per cent mortality rate (Table III). Since 1930, the mortality rate has fallen to 20 per cent for the one stage operation, but we have still not had a death following a two stage procedure, except in those cases previous to 1930 in which

the nodes had become fixed (Table III) The answer to this is early treatment before a dangerous one step operation becomes necessary and also more discrimination in the selection of cases This finding is almost universal by those who advocate neck dissections whether the original growth has been treated by radiation or surgery

Our percentage of five year cures is inverse to the number of post-operative deaths, as follows Before 1930, each patient whom we treated radically for cancer of the mouth had four chances out of five of surviving operation, and a one to two chance of remaining free of cancer for five or more years Those treated between May, 1930, and May, 1932, had a 12 to one chance of surviving operation and about an even chance for five or more years of freedom—this without excluding from treatment any patient whom we thought might have a fighting chance for a five year cure

The average course of an uncured mouth cancer entails a long period of misery and isolation for which death alone can bring relief We do not, therefore, subscribe to the logic of those who advise against neck dissections in early cancer of the lip, because it is thought that in only 20 per cent of these would the neck nodes eventually become involved Further, it is very difficult to get the average patient to return at regular intervals for examination over a long period of time, and this is apparently very necessary in cancer of the lip

It had been our former practice to postpone neck dissections for three months or more as a partial check on the control of the primary growth, but since we have been substituting the insertion of radon seeds for excision in the treatment of the latter, we have seen several uncontrollable neck metastases occur during the observation period, and believe that, for tongue ulcers at least, the dissection should, when practicable, be performed at the time of the insertion of the radium

Although many authors have indicated a distinct preference for radiation over surgery for the nodes, one can find others in general accord with the position outlined here From France, Duval and Redon² report not a single death in a year from the most radical type of block surgical excision performed for tongue cancer, Roux, Berger and Tailhefer,³ of the Curie Foundation, had but six postoperative deaths after 212 similarly radical block excisions performed before 1927, and Ducuing, Fabie and Gouzy⁴ have recorded their technic of neck dissection

The true test of an ability to cure or control mouth cancer will come only when these cases can be put under proper treatment at an early period in the disease That we are now not able to do this is suggested by our own postoperative mortality rate, and by the fact that, in spite of our present desire to perform prophylactic or therapeutic block excisions wherever possible, we have for one reason or another been able to accomplish this in less than one out of every three of 750 cases of cancer of this region For the present we see little hope of improvement in this regard Here as elsewhere in the cancer fight, Delay, the handmaid of Failure, is the daugh-

TABLE I

SUMMARY OF A GROUP OF MIXED CASES OF PROVEN CANCER

Treated between 1930 and 1932 by One Stage Operation The Neck Dissection Being Performed at Same Operation as Treatment of Primary Lesion

Age	Duration	Location	Operation	Alive	Dead	Cause of Death	Cancer Neck Nodes	Palpable Nodes
42	6 wks	Ulcer at junction ant pillar tongue	24 m c radon and complete neck dissection and 2,400 mgh radium to area broken down nodes	5 yrs +			Yes	Yes
50	Unknown leukoplakia for 5 yrs preceding	Buccal mucosa extending on lower alveolus	Radical operation, including neck dissection	5 yrs +			No	Yes
49	2 yrs Much previous treatment including paste	Most of tongue	Radical excision of tongue because of pain, and neck dissection	5 yrs +			Yes	Yes
57	Unknown	Rt cheek, large ulcer	Biopsy followed by radical operation	3 yrs postoper		Cancer locally	No	Yes
50?	Unknown	Ulcer of buccal mucosa	Radical operation and neck dissection	5 yrs +			No	Yes

75	Unknown	Ulcer of cheek	Radical operation	5 mos	Cancer locally	No	Yes
47	2 mos (?)	Cheek and palate	Radical operation	7 mos	Cancer	No	Yes
49	4 yrs	Tongue (most of dor- sal surface)	Excision of tongue and bilateral upper neck dissection	15 da	Pneumonia	Yes	Yes
69	6 mos	Buccal fornix	Radical operation	8 da	Hemorrhage	No	Yes
51	1 yr	Alveolar process, also had leukoplakia both cheeks	Radical operation rt side in Sept, 1931 De- veloped a second and apparently new growth on left lower alveolus and had radical op on left side April, 1932	8 mos following first oper	Cancer	Neck nodes neg- ative first op Positive at sec- ond	Yes
47	6 mos	Left half of tongue	36 m c radon to tongue and complete neck dis- section	4 mos	Cancer	Yes	Yes

11 cases

Two postoperative deaths

Four cases five year cures, 36.6 per cent

TABLE II
SUMMARY OF A GROUP OF MIXED CASES OF PROVEN CANCER
Treated Between January, 1930, and May, 1932, the Neck Dissection Being Performed Subsequent to Treatment of Original Lesion

Age	Duration of Lesion	Location	Operation	Alive	Dead	Cause of Death	Cancer Neck Nodes	Palpable Nodes
61	Unknown	Under surface tongue, 1 cm ulcer	Biopsy and 18 m c radon 3 mos later, complete neck dissection		2 yrs	Cancer	Yes	Yes
64	Unknown	1½ cm ulcer junction ant pillar and tongue	Biopsy and 18 m c radon 4 mos later, complete neck dissection		1 yr	Cancer	Yes	Yes
57	7 mos	Tonsillar fossa extending over ramus of mandible	Biopsy and 21 m c radon, neck dissection 5 mos later		2 yrs	Apoplexy No cancer	Yes	Yes
60	Unknown	Junction of tongue and floor of mouth 1½ cm ulcer	Biopsy and 24 6 m c radon 9 mos later, complete neck dissection		1 yr	Cancer	Yes	Yes
73	12 yrs	Hole through cheek with ulcerated border	Cautery excision 1 mo later, neck dissection		4 yrs	Cancer Local involvement	No	Yes

67	1½ mos	Ulcer 2½ cm long, alveolar process and palate	Biopsy and 18 m c radon 5 mos later, neck dissection	5 yrs +	Yes	Yes
?	Unknown	Ulcer of cheek	Cautery excision 9 mos later neck dissection	5 yrs +	No	Yes
73	2 yrs	Ulcer face, 5½ cm	Cautery excision 9 mos later, neck dissection	5 yrs +	Yes	Yes
61	Unknown	Lip origin, healed by excision elsewhere	Bilateral neck dissection	5 yrs +	Yes	Yes
53	1 yr	Large ulcer junction ant pillar and tongue	Biopsy and 18 m c radon 6 mos later, complete neck dissection	5 yrs +	No	Yes
45	2 mos (?)	Most of rt border of tongue	Biopsy and 27 7 m c radon 4 mos later, complete neck dissection	5 yrs +	No	Yes

11 cases
No operative mortality
Six cases five year cures, 55 per cent

TABLE III
COMPARATIVE SUMMARY OF 153 CASES OF ORAL CANCER*

Length of Time	Type Operation	Number Cases	Number Post-operative Deaths	Living Five Years or More	Cures	Percentage of Cures	Post-operative Deaths	Untraced	Combined Postoperative Percentage, Both series
1930 to May, 1932	2 stage	11	0	6	6	55%	0	None	8 % death rate 45 4% cures
1930 to 1932	1 stage	11	2	4	4	36 6%	18%	None	
Before 1930	2 stage	61	3	28		46%	5%	(10 out of 21 infected nodes, and 18 out of 26 noninfected, survived 5 years or more)	
Before 1930	1 stage	70	24	16		23%	34%		21% death rate 34% cures

(29 cases neck nodes negative, 6 cures, and 40 positive, 10 cures)

(One chance out of 5 of a P O death, and 1 out of 3 of a 5 year cure)

Total of all cases to May, 1932—153 cases 29 P O deaths, 54 five year cures

19% deaths, 35% cures

Every case of cancer of face or mouth given radical treatment

From 1915 to 1930—Had 1 in 5 chance for P O death and a 1 in 3 chance for a five year cure

From 1915 to 1932—Had 1 in 5 plus chance for P O death and better than a 1 in 3 chance for a five year cure

From 1930 to 1932—Had 1 in 11 chance for P O death and near a 1 in 2 chance for a five year cure

But one recurrence in neck after dissection of nonfixed to carotid or mandible nodes (2 per cent)

Not much difference in cures between infected and noninfected nodes

* A few cases of advanced lip cancer with microscopically proven metastases of the lymph nodes have been included as oral cancer

ter of Indecision, which latter but reflects our widespread lack of authoritative knowledge of what, when, and how to do, and what the present standards of oral cancer control should be

The ultimate responsibility for all this rests not upon the isolated practitioners of medicine and surgery who usually first see or treat such cases. but with the leaders of surgery, who should have more than an academic interest in this subject, and, as a body, have failed to make either investigation or pronouncements of sufficient depth or unanimity to bring the situation under control. Isolated leaders have pointed the way, Whitehead, Butlin, Kocher, Crile, Roux, and many others have, in turn, carried on an almost continuous demonstration of methods of treatment, and of the high curability of intra-oral cancer, reaching, in point of time, from popularization of the radical breast operation down to the present day. It is difficult to say why the one should have been so early standardized and so universally adopted—its ritual and its circumstance being treated as a holy tradition—while the other was left to shift largely for itself like an unwanted child, unless it be the proximity of the one to the abdomen upon which most all surgical thought was for the time centered.

Twenty-eight years ago, Butlin⁵ published a complete and informative statistical analysis of 197 cases of cancer of the tongue, with a high percentage of three or more year cures and a low operative mortality. This should have served as an inspiration in practice, and a model of form for subsequent authors to follow, but it seemed to have awakened as little general appreciation in his day as it commands in ours. A cursory analysis of 850 recent articles on the treatment of cancer of the mouth, supplied from the library of the American College of Surgeons, reveals a small percentage of informative communications (Table IV). From its somewhat difficult perusal

TABLE IV
848 CARD REFERENCES FROM THE AMERICAN COLLEGE OF SURGEONS FILES
Listed According to Title Regarding Treatment for Carcinoma

Operation		Radiation	Combined	Indeterminate
Carcinoma of lymph nodes	25	3	2	20
Pharynx	6	17		24
Tongue	10	25	5	55
Neck	1	2		16
Larynx	79	60	8	137
Nasopharynx	0	3	1	40
Mouth	16	39	4	106
Lip	9	17	4	54
Face	10	8	5	37

two impressions stand out forcefully. One, regret for the tremendous waste of opportunity which it unwittingly depicts, and the other, that the present disastrous feeling of uncertainty could be radically changed in a relatively

short time through the accurate information that might be made available if this or some other authoritative surgical body would devise, popularize and distribute a simple, usable and uniform plan for observing and recording the conditions found, the treatment given, and the results obtained in true cancer of the mouth, whether a man has treated one, or a series of a hundred cases

The American College of Surgeons is furnishing, on request, and filing for reference, a special record blank for registering each treated case of cancer of the mouth. It might not be practical to fill out this quite elaborate form completely in the majority of cases, however, if such blanks were accurately filled for only a small percentage of the various series of cases that will be treated in the next few years, even with only the essential facts of the location and the stage of advancement of the disease, the clinical and microscopic diagnosis, the plan of treatment of both the primary disease and the lymphatic drainage areas, the operative death rate and the percentage of freedom from recurrence three or five years, or more, much of the uncertainty which now influences the choice of treatment of true cancer in this area could be dispelled within a reasonable period of time

REFERENCES

- ¹ Blair, V P, and Brown, J B The Treatment of Cancerous or Potentially Cancerous Cervical Lymph Nodes ANNALS OF SURGERY, 98, 650-661, October, 1933
- ² Duval and Redon Jour de Chir, 45, 711, May, 1935
- ³ Roux, Berger and Tailhefer Presse med, 41, 482, March, 1933
- ⁴ Ducuing *et al* Jour de Chir, 45, 849, June, 1935
- ⁵ Butlin Brit Med Jour, 1-6, January 2, 1909

EPITHELIOMA OF THE LOWER LIP

A SUGGESTED ROUTINE FOR TREATMENT WITH DESCRIPTION OF THE
OPERATIVE EXCISION OF THE SUBMENTAL AND SUBMAXILLARY LYMPH NODES

ROBERT H. KENNEDY, M.D.

NEW YORK CITY, N. Y.

FROM THE TUMOR CLINIC, SKIN AND CANCER UNIT, NEW YORK POST GRADUATE MEDICAL SCHOOL AND HOSPITAL
COLUMBIA UNIVERSITY, NEW YORK CITY, N. Y. DR. CARL EGGER, ATTENDING SURGEON

IN a previous article¹ the necessity of surgical extirpation of the lymph drainage area in patients with squamous cell epithelioma of the lip was emphasized, following the same rules which would be used in any other cancer which metastasizes to regional nodes practicable of removal. The argument continues as to whether neck dissection should be effected when nodes are not palpable. The reasons advanced for and against this have been excellently summarized by Pflueger.² Of 30 men in this field whom he contacted, the proportion was two to one against prophylactic excision. However, it must be noted that those recorded against this were almost invariably radiologists, while those in favor were equally preponderantly surgeons. We shall not add to the argument in this presentation, but merely state that we still believe that, in general, neck dissection should be performed whether or not nodes are palpable.

One objection raised to the neck operation is its high mortality. In a reported series¹ this was given as 11.4 per cent. At that time we usually performed a block dissection to the omohyoid crossing of the jugular vein. On further analyzing our operative mortality, in a series which now consists of 339 patients, it was found that the majority of deaths occurred when some more extensive procedure was undertaken, *e g*, a bilateral block dissection at one operation, an extensive plastic procedure on the lip or a partial resection of the jaw. There were 163 patients who had block dissections to the omohyoid crossing, with no more extensive procedure on the lip at the same operation than a V excision. There were nine deaths. This should really represent our mortality in block dissections of the neck and amounts to 5.5 per cent. Since bilateral block dissections were effected on many patients at two operations, these 163 patients had 214 block dissections. One might therefore consider the mortality of this operation 4.2 per cent.

This includes patients with enlarged nodes, both involved and not involved, and nonpalpable nodes, both involved and uninvolved. We believe it is fairer to take the whole group, as representing the average mortality in block dissection, than to limit it merely to those cases in which a prophylactic dissection was performed, although the latter figure might be somewhat lower. We felt that a mortality rate of 5.5 per cent left a considerable opening for argument against prophylactic neck dissection to the omohyoid crossing.

Of the 163 patients, there were nine hospital deaths, 19 were lost from follow up under one year, 48 have remained well between one and five years, 56 have remained well over five years, eight died of other causes after a period of over five years, eight died within five years of cancer, eight died within five years of unknown cause and seven died within five years of other causes

We then analyzed the site of lymph nodes found involved at the pathologic examination. Metastatic involvement occurred in 21 per cent of the instances in which neck dissections to the omohyoid crossing were performed. In 46 cases the specimen had been so marked that it was possible for the pathologist to report the exact site of involved nodes. In 40 this involvement was limited to the submaxillary or submental regions. In the remaining six all showed evident clinical involvement with carcinoma in the neck before operation. Carcinoma was never found in nodes other than the submaxillary or submental, when lymph nodes were not palpable before operation.

TABLE I
LOCATION OF METASTATIC LYMPH NODES

Submental and both submaxillary regions	2
Submental and one submaxillary region	2
Both submaxillary regions	4
One submaxillary region	31
Submental region	1
Submaxillary and carotid node (ulcerating and attached to jaw)	1
Submaxillary and parotid regions	1
Submaxillary region and other nodes on same side of neck	1
Extensive involvement	3
Totals	46

Three patients who had no palpable nodes, and upon whom no primary neck dissection was effected, later developed metastases. Two were in the submaxillary and one in the submaxillary and submental regions.

Figi³ states "Extension of the malignant process through the lymph vessels draining directly into the deep cervical nodes or those entering the mental foramen rarely occurs, so that removal of the cervical nodes along with the submental and submaxillary groups is scarcely justifiable as a routine procedure." From a review of the literature, among those who perform neck dissections, the majority apparently prefer submaxillary and submental excision only.^{2 3 4 5 6 7 8 9} Some make the operation more extensive when metastatic involvement is found.

At present we believe that submaxillary and submental excision is required in those patients in whom we think that there is no evidence of metastases. When we believe that metastases have occurred or when they are found in the suprathyoid operation, a block dissection to the omohyoid crossing should be performed.

The upper neck operation has been undertaken in our clinic 45 times

with no mortality. This should be compared with 55 per cent for dissections to the omohyoid crossing. The follow up is not sufficiently long to be of any value as yet. The patient remains in the hospital less than a week, the lip cancer being excised at the same operation. We have used rectal anesthesia, although we believe that local anesthesia is probably feasible. The scar is not unsightly. Figi's³ mortality for this operation was 0.18 per cent in 549 patients. In only 16.53 per cent were the lymph nodes involved. In his patients in whom no lymph node involvement was found, 89.74 per cent lived five years or more, where involvement was found 39.13 per cent lived five years or more. Statistically the odds seem to be all in favor of a suprahyoid excision when metastases are not definitely present on account of the low operative mortality, the site at which metastases first appear, the low morbidity and the long period of freedom from disease. I can find no justification for radiation therapy alone, to the neck, and no longer can I justify a block dissection to the omohyoid crossing as prophylaxis.

On the basis of these findings, we have adopted in our clinic the following routine for treatment of epithelioma of the lower lip.

Suggested Routine—(1) All local lesions shall have a biopsy or excision.

(2) Lesions not over 1 cm in diameter, without deep ulceration, without infiltration apparently extending to muscle, without palpable nodes in the neck, of Grade I, and of comparatively brief duration, may be treated locally only on the responsibility of the surgeon. The lesion must fulfill all the above requirements.

(3) The local lesion may be treated either by surgery or radiation.

(4) If nodes are not palpable, or if the surgeon does not believe palpable nodes contain metastases, a block dissection of the submental and one or both submaxillary regions shall be effected at one operation. One side only may be undertaken in case the lip lesion is in the lateral third only.

(5) If metastases are found in this dissection, a further block dissection shall be performed to the omohyoid crossing on the side involved.

(6) If palpable nodes are present, and believed to contain cancer, the patient shall have a block dissection of the nodes of the neck to the omohyoid crossing.

(7) If the lesion is in the middle third of the lip this dissection shall be bilateral and undertaken by two operations.

(8) If the surgeon considers that the general condition of the patient does not warrant a possible 55 per cent operative mortality for block dissection to omohyoid crossing against at least a 20 per cent cancer mortality, he may treat the lesion locally only, stating his reasons on the chart.

(9) If nodes other than submental and submaxillary are found involved the remainder of the lymph drainage area down to the clavicle shall be excised.

(10) Any operative procedure undertaken upon patients with fixed nodes

shall be considered experimental and palliative only. Otherwise these patients shall receive radiation therapy, if the radiotherapist consents, for palliation only.

(11) Follow-up observation shall be monthly for the first year, every two months for the second year, every three months for the third year and then every six months for the duration of life.

Excision of the submaxillary and submental nodes only has apparently been a common operative procedure since the last quarter of the nineteenth century. Yet I have searched almost in vain for a detailed description of it. Judd,¹⁰ in 1908, gave a brief account. Ducuing, Fabre and Dambrin,¹¹ in 1935, presented an excellent detailed discussion of a similar operative procedure to that which I shall describe. However, there are important points of difference. They apparently employ this in cases in which they believe involved nodes are present, where I think it should never be used. They do not remove the platysma muscle, whereas we have found metastases in this structure. They remove the digastric and stylohyoid muscles and the carotid node, which I think is unnecessary. The operation which we shall describe is a portion of the block dissection as described by Semken.¹² It follows his idea of sharp fascial dissection leaving only red muscle exposed in the depth of the wound. Its extent is guided by landmarks which can be found easily, if further excision is necessary, without retracing one's steps. The portion of the excision from the lower margin of the mandible upward is necessary only if involved nodes are found, but should always be done to save uncovering the same area a second time should they be found. Careful hemostasis is necessary throughout the procedure, so that fascial planes may be followed readily.

Operative Procedure in Bilateral Dissection of the Submaxillary and Submental Lymph Nodes

(1) Incision—A transverse incision is made at the level of the hyoid bone, following a natural fold of the neck and extending to one centimeter beyond the anterior border of each sternomastoid muscle. The incision is deepened to the platysma muscle.

(2) The upper flap is raised superficial to the platysma muscle to the level of the upper borders of the mandible in the region of the facial vessels and sloping gradually to the point of the jaw in the median line and to the angle of the jaw posteriorly. The lower flap is raised for about one-half centimeter in order to facilitate the later suturing of the incision.

(3) Outline the Area to Be Removed—The platysma and the fascia over the digastric muscles are incised along the line of the skin incision. An incision is made to the periosteum of the mandible along the line to which the upper flap has been dissected back, tying the facial vessels on each side at this level. Carry the fascia over the masseter muscle down to the lower border of the mandible and identify the space between the submaxillary and parotid glands. This is usually marked by the posterior facial vein which can be preserved. A longitudinal incision is made immediately in

front of the posterior facial vein, connecting the upper and lower outlining incisions Tie off the anterior facial vein just proximal to its junction with the posterior facial vein

(4) Dissection of the Submental and Submaxillary Spaces—This dissection is most easily carried out from before backward This is difficult if the excised mass is kept in one piece It is more practical to divide the mass along the border of the anterior belly of one of the digastric muscles and there dissect in two portions If the entire area to be removed has been outlined to its full depth before this is done, the likelihood of spreading metastases, through cutting across the field on the anterior belly of the digastric muscle, is minimized

“(A) Dissection of Submental Space¹²—The upper attachment of each anterior digastric belly is exposed first, to establish the position of these muscles, then a longitudinal incision is made along the anterior digastric belly of the opposite side, and this is continued to the cornu of the hyoid It should be deepened to fully expose the deep muscle and fascial plane The removal of the fat and lymphatic mass begins at the fascial cut along the digastric belly of the opposite side, and it proceeds from side-to-side across the mylohyoid muscle floor of this space (including its fascia), and then across the anterior digastric belly of the proximal side The apex lymph node of this group is usually deeply placed under the symphysis of the chin, in a pocket at the angle between the two anterior digastric muscle bellies, and it is easily overlooked unless special care is exercised to remove it

“(B) Dissection of the Submaxillary Space—The mass of platysma, blood vessels and fascia is then dissected downward to the ‘subcutaneous’ edge of the lower jaw A light incision of the fascia along the mandible then opens the submaxillary space, and with the handle of the scalpel, the submaxillary gland and the related lymph nodes are gently pushed downward and away from the roof of the space A rich vascular plexus is found on the masseter Care must be exercised, also, in opening the submaxillary spaces, to avoid injuring the fine, troublesome vessels from the mylohyoid branches of the internal maxillary artery and the related veins The dissection of the submaxillary space is then begun anteriorly, and proceeds from before backward, beginning at the anterior belly of the proximal digastric muscle, where the submental lymphatic dissection ended The dissected tissue mass is then carried over the lateral part of the mylohyoid muscle Next, the lateral edge of this muscle is drawn toward the midline with a blunt retractor, and the deep anterior part of the submaxillary salivary gland is mobilized Above it, in the depth, the lingual branch of the third (mandibular) division of the trigeminus nerve may be recognized, as a large nerve A branch that extends from this nerve to the salivary gland is divided Beneath the submaxillary gland, the hypoglossal nerve is recognized on the outer surface of the hyoglossus muscle, as it proceeds obliquely upward to the tongue It is accompanied by the ranine vein The sub-

maxillary duct (Wharton's) with the small collar of gland substance and some blood vessels, is divided between clamps, and the gland, together with the adherent lymph node groups of the submaxillary space, is gently raised from the floor of the space and dissected back until the external maxillary artery is reached in the posterior part of the space. The artery and an accompanying vein are ligated or clamped at the upper border of the posterior belly of the digastric and the stylohyoid muscles, and divided." The dissection is completed by removing the fascia from the tendon and posterior belly of the digastric muscle. This leaves, in the base of the field, the mandible covered by periosteum, the masseter, mylohyoid and digastric muscles denuded of their fascia, the lingual and hypoglossal nerves and the hyoglossus muscle in the depth of the submaxillary space. The submaxillary space of the opposite side is cleaned out in the same way.

(5) The wound is closed by interrupted sutures, care being taken to include the stump of the platysma muscle with the skin of the lower margin of the incision.

(6) A drain is inserted into each submaxillary space.

(7) Pressure dressing.

Procedure in Unilateral Dissection

(1) A transverse incision is made to the median line only and then carried longitudinally upward from the level of the hyoid bone to the point of jaw. After raising the flap as in the bilateral operation to above the margin of the jaw, the longitudinal incision is undermined toward the opposite side sufficiently to expose the anterior belly of the opposite digastric muscle. This makes it possible to perform a block dissection of the whole submental space. One then proceeds as in the first part of the bilateral dissection.

SUMMARY

(1) In epithelioma of the lower lip, conservative treatment demands the removal of the lymph drainage area whether or not evident metastatic involvement of the lymph nodes is present.

(2) When lymph nodes were not palpable before operation, metastases were never found present except in the submental or submaxillary nodes.

(3) Whenever involved nodes were found in other regions, clinical evidences of metastases were invariably definite before operation.

(4) In some patients who failed to have neck dissections effected, metastases developed, while under observation, in the submental or submaxillary regions first, never elsewhere.

(5) Where there is no clinical evidence of metastases, we believe that block excision of the submental and submaxillary nodes is sufficient.

(6) The mortality of this operation is low, the morbidity brief, and the scar not unsightly.

(7) If involvement of the submental or submaxillary nodes is present,

no arrest of the disease can be expected from this limited operation. More extensive excision must be undertaken.

(8) A routine for handling these patients is suggested. This has been in use in our clinic for the past three years.

(9) A detailed description of the suprahypoid operation is presented.

REFERENCES

- ¹ Kennedy, R. H. *ANNALS OF SURGERY*, 99, 81, 1934
- ² Pflueger, O. H. *Calif and West Med*, 39, 391, 1933
- ³ Figi, F. A. *Surg, Gynec, and Obstet*, 59, 810, 1934
- ⁴ Fenwick, P. C., and Hines, C. F. *New Zealand Med Jour*, 32, 53, 1933
- ⁵ Dixon, C. F. *Surg Clin N Amer*, 15, 1303, 1935
- ⁶ Fischel, E. *Surg, Gynec, and Obstet*, 60, 505, 1935
- ⁷ Jose, I. B., and McCoy, H. A. *Med Jour Australia*, 21, 712, 1934
- ⁸ Stacy, H. S. *Med Jour Australia*, 21, 712, 1934
- ⁹ Bartlett, E. I., and Callander, C. L. *Archiv Surg*, 16, 1214, 1928
- ¹⁰ Judd, E. S. *Old Dominion Jour Med and Surg*, 7, 339, 1908
- ¹¹ Ducuing, J., Fabre, P., and Dambrin, P. *Tech Chir*, 27, 1, 1935
- ¹² Semken, G. H. *Nelson's Loose Leaf Surgery*, 2, 862. Thos Nelson & Sons, N. Y., 1932

THE RESULTS AND METHODS OF TREATMENT OF CANCER BY RADIATION

PROFESSOR HENRI COUTARD, M D

PARIS, FRANCE

(I) SURGERY AND CANCER—That the most eminent surgeons of this country are interested in the hesitant beginnings of radiotherapy, and meet to discuss radiation in the treatment of cancer, is a manifestation the value of which is greatly appreciated by those who study this form of therapy. It is a great honor for the Fondation Curie and for its delegate to be invited to participate in these discussions.

It is at the same time an agreeable occasion for a radiotherapist to express his admiration for the progress accomplished in surgical technic and for the results of surgery in dealing with cancer. Also, I am pleased to recall here the names of certain American pioneers in this type of surgery, whose methods are now applied throughout the world. Among them are those of Halsted, the creator of the radical operation for cancer of the breast, the Mayos, who have transformed abdominal surgery, Cushing, who has created the surgery of the nervous system, Crile, who has perfected the technic of resection of cervical adenopathy, Graham, whose studies of operative technic for intrathoracic tumors give some hope in this domain, Bloodgood, whose works are appreciated not only by the surgeons, but by all cancerologists. Permit me to recall here a trait of Bloodgood's generous character. He was at one time skeptical of radiation. But when he began to realize the possibilities of radiotherapy in cancer, he was eager to manifest, in the presence of a large number of colleagues whom he had invited to his home, the new interest which radiotherapy henceforth held for him in the struggle against cancer. Several days after this memorable reunion, where he described his projects, death, which seems at times to wish to oppose human realizations, brusquely tore him from his work and from the affection of his family and friends.

(II) CANCER AND RADIATION—Rich only in hope, possessing only incomplete information, incapable of offering precise technics, adapted to diverse types of cancer, radiotherapy has, however, obtained definite cures in cases incurable by surgery.

While surgery has applied its efforts with a certain regularity to all neoplastic localizations, radiation has, up to the present, been applied with success only to certain regions, in certain types of cancer, in spite of repeated attempts of treatment in all the histologic forms and in all localizations. Hence a primary classification of tumors in relation to the results of radiotherapy tends, little by little, to be established by regions, and according to a precise topography of the points of origin. Thus in the buccal cavity, the larynx and pharynx, there exist neoplasms of frequent curability, when

the origin is situated at a definite point. But when the point of origin is several millimeters distant, even though the histologic form is almost similar failure is the rule. We shall later cite examples of this.

This empiric classification, when widely established, will give more living reality to histologic classifications, on which treatment by radiation was able, in the very beginning, to find a foothold, and will continue to strengthen. From the very beginning of radiotherapy, in the course of the year 1919 in particular, Regaud declared that radiation would be efficacious only in certain histologic forms. Without this scientific conception, without this foresight of facts, all progress would have been most difficult, and the discouragement in the presence of repeated failures in some histologic forms would have paralyzed for a long time the development of radiation.

(III) RESULTS OF RADIATION IN THE TREATMENT OF CANCER.—The patients who comprise the following statistics have been treated either by roentgenotherapy in our service, or in the ensemble of the different services of the Curie Institute, by association of radium and roentgen rays for the uterus and parametria, or by the association of radium and surgery for the tongue. Patients considered as cured have been followed for a minimum of five years. In fact, local recurrences have been exceptional after this period of control, but metastases by blood or lymphatic routes have not been rare after five years, when the neoplastic localizations were accompanied by adenopathy.

(a) *Lymphosarcoma of the Pharynx*.—We cite here statistics gathered by Doctor Jutras of Montreal, on the subject of patients treated, from 1923 to 1928, by roentgenotherapy in our service. Forty-six patients were irradiated, 16 have a minimum survival of five years, or 34 per cent.

(b) *Epitheliomata of the Palatotonsillar Region, Larynx and Pharynx*.—These statistics comprise the cases irradiated in our service, from 1920 to 1930, by roentgenotherapy. Sixty-six patients with epitheliomata of the palatotonsillar region were treated, 21 have a minimum survival of five years, or 32 per cent.

One hundred twenty-six patients with cancer of the larynx were treated, 31 have a minimum survival of five years, or 24 per cent.

Two hundred twenty-five patients with cancer of the pharynx were treated, 26 have a minimum survival of five years, or 11 per cent.

(c) *Epitheliomata of the Maxillary Sinus*.—At the Fondation Curie, the majority of epitheliomata of the maxillary sinus have been treated surgically, followed by application of tubes of radium in the cavity (method of Hautant-Monod). The results have been sufficiently satisfactory that the use of external radiation has in general been discontinued. However, when the extension of the lesions has rendered the cases totally inoperable, we have resorted to roentgenotherapy. The number of patients treated by roentgenotherapy is for this reason small. However, the results are favorable, and we have the impression that this type of cancer is among the most favorable from the point of view of roentgenotherapy.

From 1920 to 1932, eight patients with cancer of the maxillary sinus were treated by roentgenotherapy alone, four are still living, with a minimum survival of five years, or 50 per cent

The first patient was treated in 1922, the second in 1930, the third in 1931, the fourth in May, 1932. Of these four cases, three had a total destruction of the floor of the orbit, and partial destruction of the malar bone, one of them had an extensive submaxillary adenopathy

(d) *Epitheliomata of the Cervix Uteri*—The statistics of cancer of the cervix are those of Lacassagne, which he has submitted to the League of Nations. They include all the cases of epithelioma of the cervix treated in the services of the Fondation Curie, by radiation, from 1919 to 1930

Nine hundred eighty-four patients have been treated. Three hundred eleven have a minimum survival of five years, or 31 per cent. These cases are divided as follows:

Degree I, 97 patients treated, 59 having a survival of 5 years, 60%

Degree II, 362 patients treated, 145 having a survival of 5 years, 50%

Degree III, 411 patients treated, 101 having a survival of 5 years, 24%

Degree IV, 112 patients treated, 6 having a survival of 5 years, 5%

By years the extremes of results have been:

Degree I, in 1921, 14%, in 1929 and 1930, 72 and 75%

Degree II, in 1919, 16%, in 1923 and 1930, 52 and 56%

Degree III, up to 1921, 0%, in 1925, 1928 and 1930, 37%

Up to 1921, cancers of the cervix were treated by radium alone, introduced into the uterine canal and vagina. In the course of 1922, the association of roentgenotherapy and radium began (the roentgen rays in general preceding the application of intracavitary radium), which has given since 1925, 37 per cent five year survivals in Degree III.

In 1924, several patients with Degrees III and IV cancer were treated by roentgenotherapy alone, without intracavitary radium, as were those cases of postoperative recurrence. Sixty-three patients were thus treated by roentgenotherapy alone, nine have a survival of more than five years, or 14 per cent. Eleven were thus treated by Baclesse, in 1930, five are still living, or 45 per cent.

These results have been obtained with 200 kilovolts, while in general this voltage is too low to obtain cancericidal doses at a depth without provoking cutaneous injuries.

(e) *Epitheliomata of the Tongue*—We give here the statistics of the Fondation Curie, comprising cancer of the tongue treated by association of radium puncture or intra-oral moulage for the primary lesion, with roentgenotherapy, radium or surgery for the adenopathy. These statistics are those of Roux-Berger, published in 1932, comprising the patients treated from 1919 to 1928. These epitheliomata are divided into three groups:

Epitheliomata of the dorsal anterior tongue

Epitheliomata of the dorsal posterior tongue

Epitheliomata of the infralingual aspect or floor of the mouth

These patients are further divided into four degrees according to the extension of the lesions

Degree I, comprising lesions of 20 Mm as a maximum

Degree II, comprising lesions involving less than one-half the tongue

Degree III, comprising lesions of more than one-half the tongue or floor of mouth

Degree IV, comprising lesions involving the totality of the tongue or floor of the mouth

Three hundred eighty-two patients have been treated, 71 have a survival of five years, or 18 per cent

Among 198 patients with epithelioma of the dorsal anterior tongue, 45 have survived five years, or 22 per cent

Among 91 patients with epithelioma of the dorsal posterior tongue, nine have survived five years, or 10 per cent

Among 93 patients with epithelioma of the infralingual region, 17 have survived five years, or 18 per cent

The dorsal anterior epitheliomata of the tongue have given 44 per cent survivals of five years for Degree I, 22 per cent for Degree II, and 10 per cent for Degree III

The dorsal posterior epitheliomata of the tongue have given 25 per cent survivals of five years for Degrees I and II, and 14 per cent for Degree III

Degree IV in these two localizations has given 2 per cent (1 in 60)

The proportion of deaths from adenopathy alone before five years, the primary lesion remaining healed, has been

24 per cent for the dorsal anterior epitheliomata

17 per cent for the dorsal posterior epitheliomata

7 per cent for the infralingual epitheliomata

The treatment of cancer of the tongue by roentgenotherapy alone has, up to the present, failed to give satisfactory results. It is, however, true that the patients treated were those having the whole of the tongue invaded, often with bilateral adenopathy, having Degree IV extent. Among 112 patients treated, only four have lived more than five years (3.5 per cent), and only nine have lived more than three years. In several cases in which marked improvement appeared to have been obtained, the patients have died of pyemia during the first year.

(IV) METHODS OF TREATMENT BY RADIATION—(A) General Procedures of Irradiation. The exposure of the above results leads us to speak of the methods of treatment which were used. If one considers the situation of the source of energy, two general methods of irradiation exist.

The first is the method of irradiation by an internal source, the energy being introduced and maintained in a fixed position in the organism.

The second is the method of irradiation by an external source, the energy being outside the organism, the transfer of the energy being transcutaneous, through the tegument, which is the case when employing roentgenotherapy and telecurie therapy.

Each of these two methods naturally has its advantages, inconveniences and dangers, and each has an adaptation to particular localizations

The first method permits the distribution of high doses of radiation in a short time, four to ten days, to the primary lesion itself, without too great damage to the general tissues, the volume of tissue irradiated always being small. Radium puncture in the treatment of cancer of the tongue or palate, intra-oral moulage in the treatment of cancers of the buccal surface, lips or floor of the mouth, and interstitial radium in the treatment of cancer of the breast are examples of this type of irradiation. Such is the treatment of cancer of the uterus by intracavitary radium utilizing very high doses. One can thus treat the primary lesion under ideal conditions provided the neoplastic mass is of limited extent, but one is obliged to utilize a second treatment, irradiation from an external source, or surgery, for the adenopathy.

The second method has the great advantage of making possible the treatment of extensive tumors, and in general the simultaneous treatment of the primary lesion and the adenopathy. It has the great inconvenience, in extensive or deep lesions, of necessitating fields of irradiation, or surfaces of entry of the rays, having a large area, and consequently irradiating a voluminous mass of tissue. In order to avoid general or local accidents, one is thus obliged to reduce the daily doses according to the area of the fields and the fragility of the organs traversed by the rays.

Meanwhile it is necessary to apply high cutaneous doses in order to attain a sufficient dose at a depth. The result is that the duration of treatment is always much longer with the method of external irradiation than with the treatment utilizing an internal source of energy. We have never obtained the cure of relatively superficial neoplasms, such as the larynx, in less than eight to ten days, and the skin modifications were always considerable when the duration of treatment was less than 20 days. When the neoplasms are more extensive and deeper, the treatment must extend over 30 to 35 days, and when it is a question of abdominal lesions (neoplasms of the cervix and parametria), the number of fields must be increased to six at a minimum, and the duration of treatment must extend to 50 or even 60 days.

(B) Generalities on the Biologic Effects.—The biologic effects are, on first appearance, the same after irradiation by external or internal sources. These are (1) The destructive effects on the neoplastic cells, which one can observe conjointly with those produced on the normal epithelium of the mucosae. (2) The effects produced on the vasculo-connective tissue, or fibrosclerosing effects, which are at times followed by necrosis, early in the method of internal irradiation, and generally occurring much later in the method of external irradiation.

In reality the biologic effects differ widely in the time of their appearance. When one uses an internal source, with a high dose given in several days, the destruction of the neoplastic cells is most often accomplished *before* the appearance of the fibrosclerosing effects. Both effects are clearly ap-

preciable within the two weeks which follow the beginning of treatment. The early necrotic effect is generally of little importance. For example in the intracavitary irradiation of the cervix, it is not exceptional to see a variable degree of necrosis of the submucosa or of the muscle itself, but considering the thickness of the cervix this necrosis is generally of little importance. Likewise, in the tongue and palate, the phenomena of sclerosis and necrosis, immediately succeeding the disappearance of the neoplasm, are of little importance. There persists only a more or less extensive shrinkage of the tissues.

When the irradiation utilizes an external source and must absolutely respect the tissues traversed, because of the extension of the neoplasm the epitheliolytic effects are much later than in the preceding case. It often happens that the vasculo-connective fibrosclerosis *precedes* the cancericidal effects and thus suspends the neoplastic involution.

Suppose, for example, that we give the same irradiation by roentgenotherapy, with the same total dose, the same daily doses, repeated in a continuous manner each day for 35 to 40 days, to the buccal cavity of three different patients having an epithelioma of the palatotonsillar region. Supposing these three epitheliomata are of the same extent and aspect, but cover in one case the tonsil, in the next the pillars and the lower part of the palate, and in the third the base of tongue and the glossopharyngeal sulcus. The first two cases have a similar histologic form, cells having little differentiation, the third case is formed of more differentiated cells. The first case is accompanied by an extensive adenopathy, unilateral on the side of the lesion, the two other cases have no adenopathy. One might think that these three epitheliomata, quite close in structure, would react essentially in the same manner to radiation. In fact, when such lesions are of small volume and can consequently be treated by radium puncture, they are frequently curable, but the treatment by an internal source of energy brings to light no differences in their properties and their sensitivities to radiation. It is otherwise following treatment by roentgenotherapy. After 20 to 25 days of treatment by roentgenotherapy, there remains in the first case only a small, round neoplastic mass of one-half a centimeter in diameter, situated on the tonsil itself. It is the point of origin of the epithelioma. With the continuation of the irradiation up to about 40 days, the disappearance of this residuum is definite at about the thirtieth to thirty-fifth day, and the disappearance of the adenopathy will occur later, about the fiftieth day. In such a case a cure may be anticipated. We have patients of this nature in whom a cure has been maintained for more than five years, and there is no appreciable modification of the vasculo-connective tissue covering the tonsil.

In the second case, one likewise notes, toward the twenty-fifth day, that the tumor has almost disappeared, with the exception of small neoplastic nodules, nonconfluent, and only several millimeters in diameter. These nodules which, in general, correspond to the point of origin of the neoplasm and to the initial malignant cells, are *not* situated on the tonsil.

as in the preceding case, but on the internal surface of the anterior pillar. Between the twenty-fifth and thirty-fifth days, one notes a transformation of the vasculo-connective tissue in the neighborhood of these small residual neoplastic nodules. The glossopalatine muscle loses its softness, becomes cicatricial, white, and deprived of vessels. This fibrosclerotic transformation is at times very marked *before* the disappearance of the neoplastic cells. One has the impression that a cure has been accomplished. But five to six months later, the pillar is covered with small multiple ulcerations, the recurrence is manifest, and rapidly assumes a necrotic character over a wide extent.

One is thus in the presence of two cancers of little histologic difference, as closely similar as to point of origin as it is possible to suppose, but different in the point of view of their manner of reaction to external radiation.

The third case differs further from the two preceding cases. Clinically the lesion extends more markedly into the glossomaxillary sulcus. However, as in the preceding cases, the greatest part of the neoplasm disappears after roentgenotherapy. There persists a tumoral residuum on the mucosa covering the internal surface of the angle of the inferior maxilla. At this point, where the vasculo-connective tissue more or less adheres to the periosteum, a cure has never been obtained.

In these three cases there is a slight difference in the histologic types, and a very great difference in the nature of the vasculo-connective tissue. When this tissue is loose, soft, elastic, as it is in the region of the tonsil or vallecula, the cure of epitheliomata arising in these regions is not difficult. But when the vasculo-connective tissue is dense, thick, matted, accompanied by muscular fibers, the tendency to fibrosclerosis is early and seems to *precede* the epitheliolytic effects. It thus seems that there exists an antagonism between "too early" fibrosclerosing effects and "too late" cancericidal effects. The more one tries to force the cancericidal effects by the augmentation of the daily doses, the more one intensifies the fibrosclerosing effects, thus reducing the nutrition and consequently the radiosensitivity of the neoplastic cells.

Thus the epitheliomata which have invaded compact bone, of which the periosteum is thick, serrated and dense, are among the most difficult to eliminate, and it is always at the site of bone involvement that recurrence occurs. Thus the epitheliomata of the inferior maxilla are in general more difficult to affect favorably than those of the superior maxilla.

The nature of the neoplastic cells and of the vasculo-connective tissue on which they develop are thus the two great factors determining success or failure in the course of irradiation by an external source of energy. It is in this manner that we are able to establish, little by little, according to the results obtained, an empiric classification of tumors according to their topographic and precise points of origin. On the contrary, irradiation by an internal source of energy produces almost equivalent cellulicidal effects,

whatever the degree of differentiation of the neoplastic cells and whatever the nature of the vasculo-connective tissue

One might thus be led to think that radiotherapy from an internal source could produce a cure in all forms of neoplasms of limited extent, and that radiotherapy from an external source could produce a cure in forms of greater extent and of slightly differentiated cells, developing in those regions having a loose vasculo-connective tissue. This is not entirely exact, radium puncture provokes quite frequently the appearance of adenopathy, and does so more frequently as the cells are less differentiated and hence have a greater tendency to local diffusion and dissemination by lymphatic routes. For example, the treatment of lymphosarcomata and undifferentiated epitheliomata by radium puncture has not in general given satisfactory results, except when preceded by external irradiation using large fields.

In résumé, irradiation by an internal source can be used particularly in the treatment of cancers of differentiated cells, of small volume, without adenopathy. Irradiation by an external source can be used in the treatment of extensive lesions accompanied by adenopathy, when the cells are undifferentiated or only slightly differentiated, and when the vasculo-connective tissue is soft, loose, elastic, nonfibrous, and not penetrated by muscular fibers.

These are the general rules based on the results obtained, when the method of external irradiation has been the most elementary, the least difficult—the method of continuous treatment. This is particularly simple when, for example, for a total cutaneous dose of 7,000 r/I,* the daily doses on the region of the neck are low (200 to 250 r/I), in order to avoid all excessive local and general reaction. But this method has never given us the cure of cancers of differentiated cells, developing on a dense fibro-connective tissue or having produced either muscular fixation, or adherence to bone or cartilage. In these cases the results are clearly improved when one strives to combat the early fibrosclerosing effects by the use of irradiation in periodic series, distributed at the moments of the maximum sensitivity of the neoplastic cells and not at those moments when the vasculo-connective tissue has a maximum tendency to sclerose.

The above exposé of the conditions of treatment and results concerns only the stratified epitheliomata, concerning which we have had a long experience. We shall now speak of the adenocarcinomata, which we know less well. It is more difficult to form an opinion on the effects of radiation in these tumors, because they have a different evolution than the stratified epitheliomata. The latter develop in essentially vital regions, such as the buccal cavity, larynx, pharynx and esophagus. They cause death in two or three years at a maximum, very rarely in more than three years, while the adenocarcinomata develop more often in less vital regions, and are in general less rapid in their evolution. Sometimes this evolution is very long, and one sees patients surviving after five years with neoplastic foci which have been temporarily arrested in their evolution by radiation. It seems

* r/I (with backscatter)

that the effect of the fibrosclerosis which prevents the cure of stratified epidermoid epitheliomata, treated by external irradiation, produces in the adenocarcinomata quite different results. The cells of the epidermoid epitheliomata do not remain for long enclosed within this fibrous tissue, after several months they regain their development and a rapid recurrence is manifest. On the contrary, the cells of the adenocarcinomata are able to remain enclosed within this fibrosclerosed tissue for years, and it is only two, three or five years after the irradiation that the neoplastic cells of the adenocarcinomata appear to liberate themselves from this fibrous envelope. Ewing reports the case of a woman irradiated for a cancer of the breast and considered cured. She was killed in an automobile accident many years after her treatment. An autopsy was made of the previously treated breast, and groups of neoplastic cells, living enclosed within a fibrosclerotic capsule, were demonstrated.

In addition to these very slowly developing forms, one sees, but more rarely, adenocarcinomata of extremely rapid evolution, which cause death in less than one year, either by local recurrence after surgical intervention, or by the appearance of numerous metastases. These are generally very radio-sensitive forms, reacting in a manner similar to the lymphosarcomata. It is among these forms only that we have obtained the definite disappearance of several apparently inoperable adenocarcinomata.

(V) SURGERY AND RADIATION IN CANCER—(a) *Choice of Treatment*. According to the consensus of surgical opinion, all movable cancers, or all movable lymph nodes, are operable and must be removed surgically. One considers only the technical operability. But there exists another factor, which is the true or biologic operability, chosen or rejected according to the tendency to cellular dissemination and rapidity of cellular multiplication. The more embryonal a neoplastic cell, the more movable a cancer, the more the adenopathy is superficial and movable, that is to say, technically operable, as, for example, the lymphosarcomata or very undifferentiated epitheliomata, the less is the tumor biologically operable, because around these movable lesions, there are already isolated cells in the lymphatic chains. We could cite many observations in which a very movable tumor, having been operated upon, underwent a rapid cellular dissemination, followed in several months by an infiltrating and fixed tumor.

As far as radiation is concerned, the diagnosis of the degree of differentiation of the cancerous cells, and the knowledge of the degree of fibrosclerotic transformation of the vasculo-connective tissue, appear to be the basis of choice of the treatment applicable to a given cancer. When the cells are very slightly differentiated, when the cancer develops on a loose, nonfibrous tissue, when the cancer does not intimately adhere to the deeper planes, when it conserves a certain mobility, when it is not fixed to bone or cartilage, it reacts in general as a very radiosensitive tumor, that is to say, having a greater percentage of probability of being cured by radiation.

As we have explained above, due to the tendency of rapid cellular

multiplication and their immediate dissemination, this type of neoplasm is not generally favorable for surgery, even though it is technically operable. Moreover, such a tumor is generally rejected by the surgeons because it is most often accompanied by early adenopathy.

Cancers consisting of differentiated cells, developing on fibrosclerotic connective tissue, are the forms generally incurable or difficult to cure by radiation, because of their relative lack of radiosensitivity. When they are technically operable, they belong to the domain of surgery, because the cells multiply slowly, have only a slight tendency to dissemination, and develop an adenopathy only rarely or late. Such are the two extremes of cases.

(b) *Association of Surgery and Radiation*—Between these two types of clearly defined cases, of which we have just spoken, there are an infinite number of intermediate cancers in which the diagnosis of differentiation and radiosensitivity is very difficult at present. In these intermediate cases, which are difficult to diagnose, the precise choice of treatment is less essential, and the association of surgery and radiation is often useful. This association will be necessary for a long time, because many cases will for long remain incurable by either surgery or radiation alone.

(1) *Preoperative Radiation*—Radiation has for its principal effect the destruction of undifferentiated, young, neoplastic cells with a great tendency to reproduction, its effect is much less on the older and more differentiated cells, less able to reproduce. It thus easily destroys the cells most dangerous for the surgeon, leaving unmodified the cells of slower activity. When the surgeon is convinced of the necessity of operative intervention, and the tumor is not one justifying radiation, it would be rational to irradiate first, and operate later, because there is very frequently an association of young and adult cells. Each surgical procedure in cancer would benefit accordingly from preceding irradiation, sufficient to produce the destruction of all cells which are on the point of reproduction. This would give the surgeon added security in his operation. In such a case, it would be rational, in our opinion, to administer about one-half of the dose capable of arresting the neoplasm, for example, 3,000 to 4,000 r/I on the skin, given slowly during ten to 12 days, with 300 to 400 r/I per day, through two opposing fields. The surgical intervention could be accomplished before the possible appearance of new, young cells, that is to say, before the twentieth day, and in any case before the slight skin reaction of the twenty-fifth day.

If this treatment by radiation provokes a great reduction in the volume of the tumor, which is appreciable about the fifteenth day, one would thus have the proof that the cancer was very radiosensitive, very rich in young cells, and that surgery practiced at once might have been followed by recurrence at a distance, or by metastases. Thus preoperative irradiation in general assures more favorable conditions from the point of view of sur-

gey, and at times it is possible to identify a tumor which is biologically operable or inoperable

In the case of a great and rapid reduction in the volume of the tumor the treatment could be terminated either by surgery or by radiation, according to the speed of diminution of the neoplastic mass. On the other hand, if there is not a reduction in the tumor after two or three weeks, it is preferable to proceed with surgery.

If the tumor is originally inoperable, adherent, fixed to the deeper structures, and shows slight sensitivity to the rays, a partial treatment by radiation will, nevertheless, destroy a certain number of cells, liberate the neoplastic mass from its adherence for a limited time, and thus facilitate the surgical procedure from the point of view of technical operability, as well as from the point of view of the risk of dissemination.

(2) *Postoperative Irradiation*—Postoperative irradiation may be either early or late. Early postoperative irradiation is preferably administered immediately after the healing of the tissues, about the twentieth day, while there still remains a slight degree of postoperative neoplastic activity, and while the cicatricial postoperative tissues have not as yet become sclerotic.

Irradiation is thus administered before the recurrence is apparent. But the recurrence is either certain, or only slightly probable. If the recurrence is certain, the surgical intervention being incomplete, the choice of the region to irradiate may be difficult if it concerns an extensive tumor having necessitated an extensive operative procedure, as, for example, an adenocarcinoma of the breast. It can happen that one may irradiate the region in which the recurrence will not take place. If the recurrence is only slightly probable, it seems preferable to us in this case also to wait, rather than to administer what is called prophylactic postoperative radiotherapy. A late postoperative irradiation, after the visible appearance or recurrence, seems to us preferable, as the radiotherapy is thus applied with precision over the zone where the cells are developing.

Insufficient, relatively slight radiotherapy has no other aim than to cause the disappearance of the most sensitive cells. It liberates for a time the neoplastic mass from the adhesions which bind it, after which these may reappear and the tumor again become fixed and immobile.

If the radiotherapy has been complete, with a curative aim, and if it has not been followed by success, the infiltration of the tumor by the vasculo-connective tissue is much earlier, the neoplasm seeming to unite more intimately with the surrounding tissues. If it was mobile before treatment, it becomes fixed and infiltrating. This is one of the reasons why a second treatment by radiation has always been inefficacious, except occasionally when the tumor was very radiosensitive.

There is the same sequence after surgery, if the neoplastic extirpation has not been complete. The neoplasm becomes more infiltrating than before the intervention. The result is that, if one irradiates a recurrent cancer after surgical intervention, one rarely obtains the disappearance of the neo-

plasm, because the cells have a reduced sensitivity due to the cicatricial tissue and the increased infiltration

Jolly, of the College of France, demonstrated 12 years ago by a very simple experiment, the degree of reduction in radiosensitivity following the diminution of the nutrition and exchange. The thymus of the pigeon, lymphoid organ of very great radiosensitivity, is bilateral, and each lobe has its own vessels. If one ligates the vessels of one side only, and then irradiates simultaneously the two lobes, one notes the destruction of all the lymphoid cells of the lobe wherein the nutrition is normal, while the cells have been very little modified in the lobe in which the nutrition has been reduced by ligation of the vessels. These facts explain why after surgery, as after radiation, cancers are less radiosensitive, since the section of the vessels and the fibrosclerosis diminishes the nutrition of the cells. Thus we have cures of recurrences after surgery only if the cells had originally a very great radiosensitivity or if the treatment was practiced early after the intervention. But even though the radiotherapy has been early or late after the surgery, the disappearance of the neoplasm has at times been followed by quite extensive necrosis, which begins in the region of surgical section of the tissues, and appears one or two years later. Postoperative radiotherapy is thus in our opinion less efficacious than radiotherapy applied to nonoperated tissues, it is, moreover, somewhat dangerous for the general tissues, at least when it concerns stratified epidermoid epitheliomata.

Nevertheless, statistics published in various countries inform us that postoperative radiation has been practiced with a certain success in adenocarcinomata of the breast, even when preoperative radiation had already been administered. Preoperative radiation favors the production of fibrosclerosis, surgery accentuates it, hence these two transformations of the vasculo-connective tissue greatly reduce the radiosensitivity of the neoplastic cells. Moreover, the doses given in postoperative prophylactic treatments, or in late treatments, have in general been low, 500 to 1,000 r/i to the region of the tumor. Even the cure of a cancer of the larynx or pharynx, or a cervical adenopathy, necessitates 4,000 to 5,000 r/i directed over the neoplastic cells. One may thus be astonished that the cure of cancer of the breast and its adjacent adenopathy is obtained with doses of 500 r/i, moreover, these treatments have been able to be repeated with success, one or even two years later.

The ensemble of these facts is difficult to explain. Indeed, we have obtained the cure of postoperative recurrence of cancers of the breast only after doses of 4,000 to 5,000 r/i on the neoplastic cells. In addition, during the course of numerous experiments, Regaud has shown that the disappearance of neoplastic cells of stratified epitheliomata, or of the normal epithelium of the testicle, have never been obtained by the use of repeated irradiation over one or several years. Moreover, he has shown that the parent cells of adenocarcinoma are in general less sensitive to radiation than the parent cells of stratified epidermoid epithelioma.

The opinion of Regaud, the case cited by Ewing, and several similar observations, in which the autopsies of patients treated by radiotherapy and apparently cured of adenocarcinomata have revealed neoplastic cells after five to ten years, leads one to think that the difference in sensitivity between the parent cells and the lineal cells is perhaps more marked in the adenocarcinomata than in the stratified epitheliomata. It would thus result that, in a certain number of cases, what had been considered as a cure would be only the destruction of the very fragile daughter cells, the parent cells, whose evolution is much slower, could remain enclosed within a fibro-sclerotic connective tissue for a very long time. Whatever the reasons may be, it seems to us justifiable to draw the following conclusions:

CONCLUSIONS

A primary empiric classification of tumors as to their precise anatomic points of origin will constitute, for radiation therapy, a basis for prognosis and procedure, and will lend to histologic classifications greater utility in radiation therapy.

As far as radiation is concerned, the diagnosis of the degree of differentiation of the cancerous cells, and the knowledge of the degree of fibro-sclerotic transformation of the vasculo-connective tissue, appear to be the basis of choice of treatment applicable to a given cancer.

In addition to the technical, or presumable, operability, there exists the true or biologic operability, which is one chosen or rejected according to the tendency to cellular dissemination and rapidity of cellular multiplication.

With the exception of very radiosensitive forms, relatively few in number, the cure of adenocarcinomata remains more difficult, and more rare, by radiation than the cure of stratified epidermoid epitheliomata.

Inasmuch as radiation has not as yet produced the cure of an appreciable number of inoperable adenocarcinomata over a period longer than five years, those which are technically and biologically operable should by preference be operated upon, as a rule, after a moderate external irradiation.

Cervical adenopathies in relation to highly differentiated epitheliomata of the mucosae benefit in general more from surgery than from radiation. On the contrary, adenopathies corresponding to neoplastic lesions formed of less differentiated cells belong to the domain of radiation.

In any combination of surgery and radiation therapy, it is, in our opinion, more efficacious to *precede* rather than *follow* surgery by radiation.

DISCUSSION—DR MAURICE LENZ (New York) It had been realized for a long time that large doses were essential for clinical arrest of cancer by roentgenotherapy. This could frequently not be carried out because of concomitant roentgen ray injury to adjacent normal tissues, especially in deeply situated and not markedly radiosensitive malignant tumors. Coutard reduced this handicap by applying to practice the principle of fractionating and protracting the total dosage over a longer period. This he did at the suggestion, and on the basis, of experimental work carried out on ram's testes by Regaud. In Coutard's method the entire amount of irradiation is given

over a period of several weeks, and the treatment is never repeated thus taking advantage of the full resistance of the normal surrounding tissues and before retrogressive radiation changes have taken place in them. In cases of neoplasms of the upper respiratory and digestive tracts this treatment produces such a severe reaction in the irradiated mucosa that it is temporarily denuded of its epithelium. The more important nourishing vascular and connective tissues, however, are conserved and the denuded area quickly epithelializes from the edges. Coutard has been able to arrest cancers which, up to his time, had been regarded as unsuitable for roentgenotherapy even by the most experienced radiologists. This he did by varying the daily and total dosage in accordance with careful daily clinical observation of the patient and prolonging the treatment over a period of several weeks.

Thus certain epitheliomata of the tonsil, pharynx and larynx have yielded a relatively high five year freedom from clinical evidence of cancer with his treatment, whereas this had occurred only exceptionally before his work became known. Successful application of his method has not been limited to himself, but has been repeated by all those who have followed his technique. For instance, there had not been a single instance of five year clinical freedom of cancer in those cases treated by roentgenotherapy at the Presbyterian Hospital of New York prior to 1931. Since we have applied the principles of his treatment, we have had a number of five year clinical arrests.

Roentgenotherapy as an addition to intra-uterine and intravaginal radium in cancer of the cervix, especially where the outer portions of the parametria are clinically involved, became important through his work and that of his associates, and was chiefly responsible for the remarkable increase in the number of five year clinical arrests in this group of cases at the Radium Institute in Paris. Roentgen ray injury to the intestines and bladder, which previously had frequently complicated the treatment in these cases, became rare.

In roentgenotherapy of cancer of the breast, which is still in its infancy, this treatment has already attained some importance as a preoperative measure, the operative removal being facilitated by shrinkage and increased mobility of the cancer. The two months' delay for preoperative roentgenotherapy certainly seems justified in cases with palpable axillary nodes, in view of the unsatisfactory, purely surgical five year statistics in this group of patients. The growth restraining effect of roentgenotherapy in inoperable cases is generally accepted. In postoperative roentgenotherapy the anatomicophysiological conditions rarely permit the administration of sufficient roentgen ray dosage to allow hope of permanent arrest of all cancer cells. The aim of the treatment is not permanent arrest, but retardation of the growth.

Coutard has stressed the relation which exact anatomic location of the cancer has to its radiosensitivity and prefers to classify the radiocurability of his cases more in accordance with the point of origin of the cancer than purely on microscopic structure. The bearing which the condition of the vascular and connective tissue background has on radiocurability is illustrated by the three patients with squamous cell cancer arising respectively in the tonsil, the anterior pillar of the tonsil, and the mucosa covering the oral surface of the angle of the lower jaw. In the tonsil where the connective tissue is loose and elastic, the results are good. On the posterior or inner surface of the anterior pillar, the connective tissue is denser and the results are correspondingly poorer. On the inner surface of the angle of the jaw, the connective tissue is very dense, tendon-like, and arrest by roent-

genotherapy practically never occurs. Our own clinical experience bears out the correctness of these observations as far as the relationship between results of roentgenotherapy and apparent site of intra-oral origin is concerned. Coutard has emphasized the clinical significance of producing roentgen ray sclerosis in the connective tissue surrounding the cancer. If this change takes place before all cancer cells have been destroyed, further irradiation increases the sclerosis but does not destroy the cancer. This, for instance, is what happens in the epitheliomata located on the inner aspect of the angle of the jaw. It also happens when sublethal noncancer-killing doses are administered at long intervals over a year or two. On the other hand, in slowly growing adenocarcinomata of the breast, sclerosis of the connective tissue following roentgenotherapy may so encapsulate the cancer cells as to prevent their growth for long periods of time and thus help to lengthen the survival of the patient.

He has emphasized the need for close cooperation between surgeon and radiotherapist when decision is to be made whether a patient with a technically removable malignant tumor should be operated upon or in spite of technical operability would derive greater benefit from radiation or from a combination of both. Finally, he has again pointed out that roentgenotherapy of cancer is not a simple technical procedure which may be entrusted to the inexperienced hands of anyone possessing a roentgenotherapeutic machine. On the contrary, it is a difficult clinical treatment which is influenced by the anatomic extent and location of the cancer, by its microscopic structure and the radioresistance of the normal surrounding tissue, and presupposes not only adequate equipment and familiarity with roentgen ray physics, but, above all, clinical judgment based upon careful observation of the patient under treatment.

PROFESSOR HENRI COUTARD (Paris, France) closing. Roentgenotherapy of cancer of the breast is, and probably will remain, one of the most difficult radiation problems for a long time. Mitosis and cicatrization may take place concurrently in cancer of the breast, yet treatment should, logically, be carried out only when tissues are especially radiosensitive, *i.e.*, during the first of these processes. This is manifestly not practical since it is not known when these changes take place. Postradiation reaction of connective tissue to similar dosage varies considerably, as shown by studies of mastectomy specimens removed five, 20 and 30 days after radiation. Roentgenotherapy has usually been unsuccessful where the connective tissue has shown sclerosis prior to irradiation. The marked divergence in clinical results of roentgenotherapy in cancer of the breast may be due to differences in reaction of the connective tissue.

THE EFFECT OF RADIATION THERAPY UPON INTRACRANIAL GLIOMATA

LOYAL DAVIS, M D , AND ARTHUR WEIL, M D
CHICAGO, ILL

FROM THE DIVISION OF SURGERY AND THE INSTITUTE OF NEUROLOGY NORTHWESTERN UNIVERSITY MEDICAL SCHOOL

AMONG the many advances made in neurologic surgery during the past 30 years has been the microscopic verification and classification of intracranial tumors found at operation and a correlation of the pathologic picture with the clinical course of the patient before and after operation. Today the neurologic surgeon must be able to foretell not only the precise situation of the lesion but its probable pathologic character as well.

It was natural that the roentgen ray and radium should be suggested in the treatment of intracranial neoplasms because many gliomata cannot be removed completely by surgical methods now at our command. There are numerous articles in the literature upon the technic of radiation therapy, upon the symptoms of reaction to the roentgen ray and upon the clinical course of the patient after treatment, but there is little evidence by which favorable results can be attributed directly to the effects of radiation.

The conclusions as to the benefit of roentgen or radium therapy upon intracranial tumors are still vague and poorly defined. Emphasis in the reports found in the literature has been placed upon apparent clinical improvement following radiation, but there is always the preceding surgical operation with partial removal of the tumor and its decompressive effect to be taken into consideration before any part of the improvement in symptoms can be credited to the effects of radiation therapy. The histopathologic effects of radiation upon gliomata and the survival periods of a group of tumors of the same histologic characteristics have not been compared microscopically and clinically with a similar group of untreated tumors. As a matter of fact, it has only been recently that evidence has appeared which deals specifically with the histopathologic effects of radiation upon gliomata.

There are three different ways to investigate the problems of the effect of deep radiation upon gliomata of the same type. First, tumors so treated may be compared with untreated tumors of the same type. Second, a comparison may be made of regions of the tumor which have been treated, with areas of tumor tissue remote from the primary focus of operation, which had not been exposed to radiation. Finally, the third method may consist of a comparison of biopsy material obtained at the time of operation and preceding radiation with autopsy material, or specimens obtained at a second operation, after prolonged treatment.

Of these methods of study, the second is preferable to the first or third because it permits of comparison between treated and untreated areas in the same glioma in a uniform environment. Practically, the difficulty of obtaining a specimen of the tumor totally unaffected by radiation is obvious. In

comparing treated and untreated tumors of the same type, many complicating factors must be taken into consideration, such as the duration of the neoplastic disease process in each patient, the location of the tumors, the age and physical condition of the patients, and other possible concomitant diseases of the brain. The comparison of biopsy material obtained before radiation with specimens obtained following radiation is perhaps the least desirable procedure because untreated tumors undergo marked degenerative changes with more or less severe inhibition of tumor growth which profoundly change the histologic picture. Therefore, the contrast between biopsy and autopsy material alone does not allow one to draw definite conclusions as to the effect of the radiation. It should be added that in the case of biopsy material the surgeon and the neuropathologist are not always sure whether it was removed from an outer, more normal zone, from the zone of glia proliferation, from the tumor itself, or from an area not invaded by the tumor. For example, the diagnosis of "astrocytoma," a less malignant glioma, may be made if the material was removed from the transitional zone or from an area of necrosis with glia proliferation only to have the clinical course of the patient demonstrate the inaccuracy of the pathologic diagnosis.

Comparison of Treated and Untreated Tumors—Four cases of glioblastoma multiforme, one ependymoma, and one medulloblastoma, all of which had been treated with the roentgen ray, were studied. Biopsy material obtained during the operation preceding radiation was studied in comparison with material obtained at autopsy. Two cases of glioblastoma multiforme, which had not been operated upon and which had not been treated with the roentgen ray, were also available for a comparative study.

By comparing the four glioblastomata operated upon and treated by roentgenotherapy with the two cases which were untreated, the impression was gained upon gross examination that the former were more solid tumors, which were more resistant to the cutting knife (after prolonged formalin fixation) than the somewhat softer and, in the center, more spongy untreated cases. After a detailed histologic study, it appeared that the central areas of necrosis were much larger in the roentgen ray treated cases than in the controls. In van Gieson stained preparations, the large amount of red-stained collagenous connective tissue within the necrotic areas of the treated cases was quite obvious to examination with the naked eye. Under the microscope an abundant stroma both of collagenous and argyrophile fibers could be seen in these areas. In the control cases such an increase in mesenchymal fibers was less evident, though there was a similar proliferation of the adventitia and the intima of the newly formed blood vessels with hyalinization of their walls such as was present in the treated cases. In the periphery of the necrotic areas of the treated cases there was an intense proliferation of tumor cells, apparently not inhibited by radiation. In none of the four cases of roentgen ray treated glioblastomata was there any evidence in the hemisphere which had been spared by the tumor, or in normal tissue adjacent to the tumor, of mesenchymal or glial overgrowth or marked disease of the cortical neurons.

Contrary to the generally accepted clinical opinion, the medulloblastoma appeared microscopically to be the tumor least affected by roentgenotherapy. There were only scattered areas of necrosis in the tumor mass which destroyed the left cerebellar hemisphere and there was no evidence of overgrowth of mesenchymal elements in these areas. Elsewhere the tumor showed abundance of growth and the spinal cord was in places completely invaded by tumor cells. At the periphery of the sections of the spinal cord a marked increase in collagenous connective tissue fibers was noted, which apparently originated from the proliferated fibroblasts of the pia-arachnoid.

The most marked inhibition of tumor growth was seen in the case of the ependymoma. In the periphery of the tumor only isolated nodules were preserved which exhibited the original histologic picture shown in the biopsy material. The main portion of the tumor tissue was transformed into necrotic areas, in which isolated rows of tumor cells were preserved only around blood vessels. Though there was not a large amount of collagenous connective tissue fibers, silver stained preparations revealed a dense meshwork of glial and argyrophile mesenchymal fibers. Areas of necrosis have been described as occurring in nontreated ependymomata but the extent of tumor tissue destruction was never as large as we observed in the treated case in this group.

It is difficult to decide just how much of the inhibition of the growth of the tumor in the four roentgen ray treated cases of glioblastoma multiforme was due to the effect of the roentgen rays and how much was due to the tendency of such a transformation which is commonly found in untreated tumors. Perhaps, the time factor may have played an important rôle in producing the different appearance in the histologic picture of the untreated and treated tumors. The former gave a history of clinical symptoms of not more than three months' duration, while the tumors which were operated upon and treated survived for a year and longer from the time of the first onset of symptoms.

Comparison of Radiated and Nonradiated Tumor Tissue Within the Same Brain—In one case of glioblastoma multiforme (No. 2098), there was an opportunity to compare the original tumor in the left hemisphere which had been operated upon with an isolated small tumor nodule in the central region of the right hemisphere. The latter also showed a large area of central necrosis with numerous, newly formed blood vessels in the periphery and proliferation of the intima with hyalinization of the wall of the central vessels. It differed, however, from the main tumor mass by the absence of collagenous and argyrophile mesenchymal fibers which were so abundant in the necrotic area of the tumor mass in the left hemisphere which had been operated upon and had received the direct effects of radiation therapy.

Comparison of Biopsy Material Obtained Before Radiation with Autopsy Material—This comparative study did not yield any results in the four glioblastomata. In all of these tumors it appeared that only the outer periphery of the tumor had been removed at the operation although the surgical record definitely gave evidence to the contrary. The sections showed an active pro-

liferation of neoplastic glioma cells but no areas of central necrosis. The difference in appearance in the case of the ependymoma has already been emphasized. No difference could be noted between the biopsy and autopsy material in the case of the medulloblastoma.

From a purely clinical consideration of the effect of roentgen rays upon the survival period of patients with gliomata, one may easily be misled into the belief that the effect is striking. There are many factors to be considered, however. Certainly, a comparison of the survival period between treated and untreated patients in our series shows little or no difference. In the case of the medulloblastomata, our survival periods have been so excellent that it is hard to correlate the facts with the microscopic findings in this particular case. We do not, however, have a series of untreated medulloblastomata for comparison.

If the survival periods following deep roentgenotherapy were years longer than those of the untreated patients, one would still have to consider the fact that gliomata of the same group may have dissimilar cell type characteristics. This alone might well account for the difference in survival periods and the actual value of roentgenotherapy would necessarily be difficult to judge.

The clinical and pathologic data upon the tumors included in this study are appended.

Case No. 2070—A male, age 33, had had symptoms of three years' duration. He was operated upon April 20, 1928, and a soft, gelatinous tumor mass which contained small cystic cavities was removed *en bloc* and by suction from the posterior portion of the temporal lobe.

From May 7 to 10, 1928, he received 1,500 Ma. minutes of deep roentgenotherapy, using 200 K V, $\frac{3}{4}$ Mm. Cu and 1 Mm. Al filters at a target distance of 50 cm., equivalent approximately to 2,400 R units. This was repeated in four weeks.

At a second operation January 25, 1929, a large amount of tumor tissue was removed with the Bovie electrosurgical unit from the posterior portion of the temporal lobe and again a large amount of soft tissue was removed with a suction apparatus. The tumor upon gross examination was yellow and gummy.

From February 7 to 19, 1929, the patient again received 1,500 Ma. minutes, or approximately 2,400 r units, of deep roentgenotherapy with the same technic used previously. This therapy was repeated in April and again in May of 1929. The patient died August 23, 1929, seven months after operation and four years after the onset of his first symptoms.

Pathologic Report—The right hemisphere of the brain was markedly enlarged and its gyri were flattened. The tumor destroyed most of the right hemisphere and invaded basal ganglia and the internal capsule. It extended almost to the tip of the occipital pole where cystic cavities filled with a gelatinous material were found. Localized for the most part in the center of the hemisphere, the tumor extended into the outer cortex and the pia-arachnoid in the parietal and occipital regions (Fig. 1).



FIG. 1—Case 2070. Glioblastoma multiforme. Section through brain. Tumor invading right hemisphere, formation of large cysts following anemic softening.

RADIATION THERAPY OF GLIOMATA

A section through the anterior commissure showed the tumor to be well preserved. Only scattered areas of necrosis were seen with a mild invasion of collagenous connective tissue fibers arising from the adventitia of blood vessels. The tumor cells did not show any definite arrangement but were densely packed together and most of them had elongated nuclei surrounded by a scanty cytoplasm with one main long process in the form of unipolar spongioblasts.

A section through the area of operation showed the presence of a thick membrane of connective tissue in which bundles of striated muscle fibers and bony tissue were seen. The tumor invaded this scar tissue along numerous new formed blood vessels. Areas of anemic softening were seen filled with scavenger cells. One focus of softening was densely filled with giant astrocytes (Figs 2 and 3).

A section through the cyst formation in the occipital lobe showed the cavity to be filled with debris of brain tissue. It was lined by a row of compound granular corpuscles and was surrounded by a wall of giant, monstrous astrocytes. Microscopic Diagnosis: Glioblastoma multiforme.



Fig 2—Case 2070 Glioblastoma multiforme. Biopsy material from first operation. Loose appearance of background with increase in glia nuclei. H and E stain.

Fig 3—Case 2070 Glioblastoma multiforme (autopsy material). Central area of necrosis surrounded by well preserved tumor tissue. Increase in blood vessels with thickened, hyalinized walls. Giemsa stain. Zeiss obj 3N, oc 6N.

Case No 2085—A male, age 27, whose history extended back four years, was operated upon September 10, 1928, and a large grayish tumor which was very tough and elastic was removed in part from the left frontotemporal area.

From September 22 to 26, 1928, the patient received 1,500 Ma minutes using 200 KV, $\frac{3}{4}$ Mm cu and 1 Mm al filters at 50 cm, or an equivalent of approximately 2,400 r units. This same dosage with the same technique of administration was repeated December 3 to 6, February 5 to 8, 1929. The patient returned to his work as a mail clerk in the postoffice and received no roentgenotherapy until May 11 to 14, 1931, when he received 1,500 Ma minutes using 1 Mm cu and 1 Mm al filters, 200 KV, or approximately 2,000 r units. He died on January 28, 1932, three years and three months after operation and seven years after the first symptom.

Pathologic Report—Biopsy material sections showed a marked condensation of glia nuclei in the white matter of the cerebral cortex. Judging from the size and chromatin content of the nuclei most of them were astrocytes. There was a marked condensation in glial fibers but no increase in blood vessels or connective tissue. Intermingled with the well defined astrocyte nuclei were numerous, smaller, dark staining nuclei, but it was impossible to demonstrate cytoplasm or processes surrounding these nuclei. Tentative Microscopic Diagnosis: Astrocytoma.

Upon gross examination of the brain there was an area of softening in the center of the left second frontal convolution which extended approximately 2 cm into the

white matter as a cystic cavity partly filled with gelatinous material. The tumor invaded both the right and left hemispheres, destroying the corpus callosum and invaded the third ventricle. The tumor had a grayish-black color and contained in its center large necrotic areas stained homogeneously black (Figs 4 and 5).



FIG 4—Case 2085 Glioblastoma multiforme. Coronal section through brain demonstrating tumor invading both hemispheres and final hemorrhage into tumor.



FIG 5—Case 2085 Glioblastoma multiforme. Biopsy material from first operation. Loose appearance of background, mild increase in glial nuclei. H and E stain. Zeiss obj 10 \times , oc 10 \times .

Sections through the right frontal lobe showed the cortex to be normal without any marked changes in the neurons, and no increase in the glial nuclei or capillaries. An area of softening was present in the second left frontal convolution due to a cystic formation which followed the organization of an old focus of anemic softening. It was surrounded by a thin capsule of collagenous connective tissue fibers followed by a zone of mild proliferation of fibrous glia. Adjacent to the wall of the lateral ventricle was an organized blood clot in which tumor cells were present. Part of the thalamus was destroyed by the invading tumor.

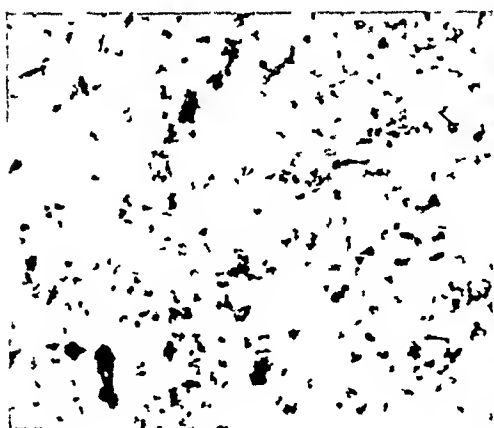


FIG 6—Case 2085 (Autopsy material). Area of calcification of newly formed blood vessels in necrotic center of tumor. Van Gieson stain. Zeiss obj 10 \times , oc 10 \times .

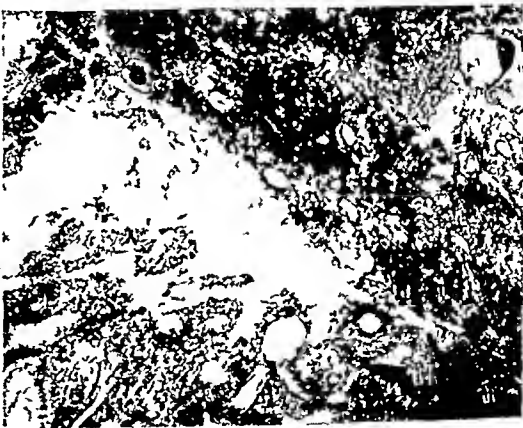


FIG 7—Case 2085 Glioblastoma multiforme (autopsy material). Tumor lining area of necrosis. Tumor cells best preserved around blood vessels. In the center increase of blood vessels with proliferation and hyalinization of adventitia. Van Gieson stain. Zeiss obj 3 \times , oc 6 \times .

The main portion of the tumor was very cellular but no definite pattern could be made out. Most of the cells showed well defined nuclei with an abundant cytoplasm but no processes. Some forms which resembled unipolar spongioblasts were seen. There was

an abundance of newly formed capillaries and the arterioles and the larger vessels appeared normal without hyalinization of their walls. In the necrotic portion of the tumor, the debris of tumor cells which showed a fine granulation of their nuclei were found. Scattered thin-walled blood vessels were surrounded by islands of better preserved tumor cells. There was no marked increase in collagenous connective tissue fibers. Microscopic Diagnosis: Glioblastoma multiforme (Figs 6 and 7).

Case No. 2098—A male, age 55, had had symptoms of 11 weeks' duration. He was operated upon April 20, 1929, and a large, soft, gelatinous tumor with a great amount of degeneration was found in the posterior portion of the right parietal lobe which was removed with the suction apparatus.

From June 3 to 10, 1929, the patient received 1,500 Ma. minutes of deep roentgen ray therapy, using 200 K V., $\frac{3}{4}$ Mm. cu. and 1 Mm. al. filters, and a target distance of 50 cm., or an equivalent approximately of 2,400 r. units. From August 6 to 14 with the same technic he received 825 Ma. minutes or approximately 1,800 r. units. From October 29 to November 5, he received the same dosage given in June, i.e., approximately 2,400 r. units. The patient died March 10, 1930.

Pathologic Report The sections obtained at operation showed a considerable increase in the glia nuclei in the white matter, acute foci of hemorrhages, but no increase in the blood vessels or areas of softening (Fig. 8).

Gross examination of the brain showed the left hemisphere to be enlarged and bulging. The tumor invaded the greater part of the left half of the brain and extended through the corpus callosum and the midbrain into the right hemisphere. The inferior half of the right temporal lobe was also invaded by tumor masses. The tumor was hard, firm, and had a reddish-gray color. There were no areas of hemorrhage within the tumor except for a small field of hemorrhagic necrosis at the base of the left frontal lobe (Fig. 9).



FIG. 8—Case 2098. Glioblastoma multiforme. Biopsy material from first operation. Mild increase in glia nuclei. H and E stain. Zeiss obj. 10x, oc. 10x.



FIG. 9—Case 2098. Glioblastoma multiforme. Coronal section through brain. Left hemisphere invaded by tumor. Isolated areas of tumor formation in right central and temporal gyrus.

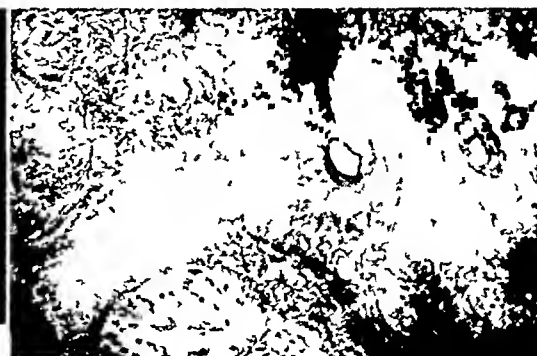


FIG. 10—Case 2098. Glioblastoma multiforme (autopsy material). Left hemisphere. Radiated tumor. Area of necrosis with increase in blood vessels with thickened and hyalinized walls and collagenous connective tissue fibers. Van Gieson stain. Zeiss obj. 3x, oc. 6x.

In sections through the area of operation tumor cells could be seen to invade the scar tissue. In the deeper layers of the section necrotic areas were present bordered by intact tumor tissue. Within these foci of necrosis there was a massive increase of collagenous connective tissue fibers and an abundance of larger blood vessels with thickened

walls which had undergone hyalinization. The tumor cells did not show any definite arrangement, though there was a tendency to radiate around blood vessels and to form palisading, streaming lines. A section through the right precentral gyrus showed a neoblastic transformation of the glia cells of the molecular layers and of the satellites of the ganglion cells layers. The latter were markedly increased in number and surrounded

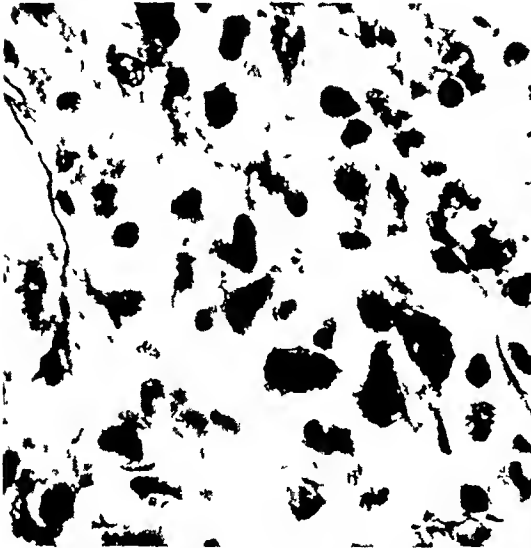


FIG 11—Case 2098 Glioblastoma multiforme (autopsy material). Tumor from radiated area in left hemisphere. Mostly tumor cells resembling unipolar spongioblasts. Davenport stain. Zeiss obj 3 Mm, oc 10x.



FIG 12—Case 2098 Glioblastoma multiforme (autopsy material). Central area of necrosis in left hemisphere. Increase in fibrillary astrocytes lying down a dense meshwork of fibers. Increase of astrocytes connective tissue fibers. Davenport stain. Zeiss obj 20x, oc 10x.

by neurons in several layers. The ganglion cells and the axis cylinders were well preserved. There was a marked increase in capillaries of the gray matter. In the white matter large areas of necrosis were seen with a mild increase in collagenous connective tissue fibers within those areas. In other places tumor cells were arranged in rosette



FIG 13—Case 2170 Glioblastoma multiforme. Tumor removed at second operation. Mild increase in collagenous connective tissue fibers. Tumor cells well preserved. van Gieson stain. Zeiss obj 10x, oc 10x.



FIG 14—Case 2170 Glioblastoma multiforme. Coronal section through brain. Invasion of left hemisphere and corpus callosum.

forms with their processes streaming toward the center of the rosettes. Microscopic Diagnosis: Glioblastoma multiforme (Figs 10, 11, and 12).

Case No 2170—A male, age 48, who had had symptoms for five months before an operation January 9, 1929, when a large, soft, degenerated tumor was removed by resection and suction from the left frontal lobe.

He received 1,500 Ma minutes of deep roentgen ray therapy using 2 Mm cu and 1 Mm al filters, 200 K V, and 50 cm target distance an equivalent approximately of 2,400 r units. The patient died November 30, 1929 nine months after operation and 14 months after his first symptom.

Pathologic Report Sections from the biopsy material showed the tumor cells well



FIG 15—Case 2170 Glioblastoma multiforme. Section through tumor (autopsy material). Increase in necrotic area, numerous newly formed blood vessels and increase in collagenous connective tissue.

preserved and surrounding islands of small blood vessels in rosette like forms. Fine collagenous connective tissue fibers and scattered fibroblasts were present. There were scattered small areas of necrosis which contained debris of tumor cells and newly formed



FIG 16—Case 2434 Untreated case of glioblastoma multiforme. Coronal section through brain. Invasion of both hemispheres by tumor.

capillaries. The tumor cells contained large, round or oval nuclei, rich in chromatin and an abundant cytoplasm which stained intensely with eosin (Fig 13).

Grossly the left hemisphere was about double the size of the right and its convolutions were flattened. The tumor invaded most of the left hemisphere, but spared the temporal lobe which was compressed and the cortex near the midline and the upper medial third

The tumor invaded the corpus callosum and compressed the striatum. The tumor was hard and firm and brownish-red in color. A small cyst was found at the posterior end of the tumor which measured approximately 2 cm in diameter (Fig 14).

Sections showed the tumor to be cellular with an abundant stroma of fibrous glia. There were scattered areas of necrosis filled with the debris of tumor nuclei and containing islands of densely accumulated coarse collagenous connective tissue fibers. Other necrotic areas were filled with fibrillary astrocytes which sent out a dense meshwork of glia fibers. Blood vessels were numerous and within the necrotic areas their walls were thickened and showed hyalinization. The tumor cells were mostly of larger types with abundant cytoplasm and eccentrically located nuclei. In Davenport stained sections forms which resembled unipolar spongioblasts were seen. Microscopic Diagnosis: Glioblastoma multiforme (Figs 15, 16 and 17).

Case No 2065—A male, age 14, who had complained of headaches for two months before an operation October 10, 1928, at which time a soft, grayish-purple tumor was found in the left cerebellar hemisphere. The tumor was removed with the suction apparatus.

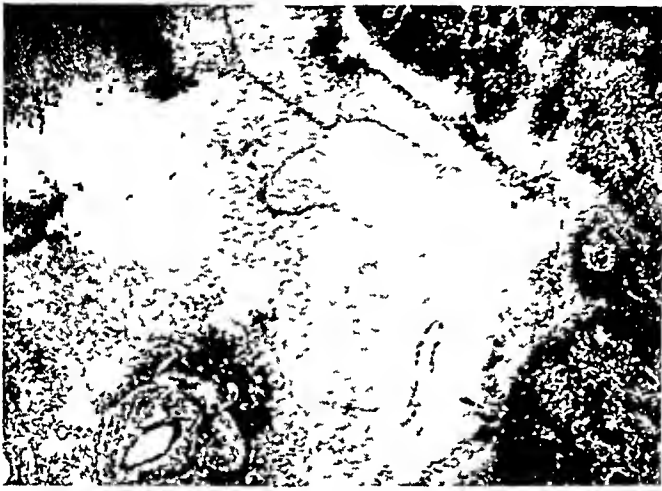


FIG 17—Case 2434. Glioblastoma multiforme. Area of central necrosis filled with debris of tumor cells. No marked increase of newly formed blood vessels or collagenous connective tissue.

He received 750 Ma minutes of deep roentgen ray therapy from October 26 to 30, 1928, using $\frac{3}{4}$ Mm cu and 1 Mm al filters, 200 K V, target distance 50 cm or an equivalent approximately of 1,200 r units. This same dosage was repeated from December 26 to January 8, 1929, and March 6 to 9, 1929. The same number of r units were given in April and in June of 1929 over the spinal column. The patient died August 16, 1929.

Pathologic Report The tumor specimen obtained at operation showed numerous densely accumulated, lymphocyte like cells with small, round, dark-staining nuclei and scanty cytoplasm.

Examination of the brain Grossly the entire ventricular system was markedly enlarged. The tumor destroyed the left cerebellar hemisphere completely and invaded the left middle cerebellar peduncle. The spinal cord was markedly enlarged at the lumbar enlargement. The cauda equina was infiltrated with tumor masses.

Part of the tumor contained islands of necrotic tissue with blood vessels around which well preserved tumor cells were clustered. There was no marked increase in collagenous connective tissue or in blood vessels. At the point of transition of the tumor into the cerebellar peduncle there was a zone of proliferated astrocytes and a mild increase in blood vessels. The tumor cells contained round, dark-staining nuclei of equal sizes, with scanty cytoplasm, and no processes. The ganglion cells of the cerebellar nuclei seen within the

tumor mass were fairly well preserved. The tumor invaded the spinal cord and there was a marked overgrowth of connective tissue and blood vessels with thickened walls. Where the tumor invaded the anterior gray matter the ganglion cells showed pyknosis and different stages of degeneration. Tumor cells also invaded the pia-arachnoid and the posterior periphery of the spinal cord. There was no increase of blood vessels or connective tissue in this area, only a mild increase in astrocytes in the immediate environment of the invading tumor. Microscopic Diagnosis: Medulloblastoma (Fig 18).

Case No. 2084—A male, age 13, was operated upon December 26, 1927, after complaining of symptoms for six months. A purple tumor mass was found to project downward into the spinal canal between the cerebellar tonsils. From January 9 to 12, 1928, the patient received 700 Ma minutes of deep roentgen ray therapy, using $\frac{3}{4}$ Mm cu and 1 Mm al filters, 200 KV, 50 cm target distance or an equivalent approximately of 1,150 r units. This same dosage was repeated by the same technic from March 12 to 15, June 11 to 14, September 11 to 15, and December 10 to 14, 1928, except that during the last treatment he received 937 one-half milli-ampere minutes or approximately 1,500 r units. The patient died March 27, 1929.

Pathologic Report Sections from the biopsy specimen showed the tumor to be very cellular. The nuclei were homogeneous and were surrounded by cytoplasm which assumed polygonal forms. The tumor cells were arranged in pseudorosette-like forms around scattered blood vessels. There was a mild increase in collagenous connective tissue interspersed between the tumor cells.

Grossly, in longitudinal sections through the brain stem and the cerebellum the tumor invaded both the right and left cerebellar hemispheres and extended as far as the roof of the fourth ventricle. The pons and medulla were flattened but not invaded by tumor masses. The tumor was solid, grayish-red in color and contained small necrotic and hemorrhagic areas (Fig 19).

The characteristic arrangement of the tumor cells seen in the biopsy specimen had disappeared. Pseudorosettes remained only in the outer periphery of the tumor. The center of the tumor was represented by large areas of necrosis which contained numerous newly formed blood vessels with thickened, hyalinized walls. Around these vessels isolated rows of tumor cells were preserved. There was a marked increase of glia fibers and an overgrowth of newly formed fibroblasts without, however, a large production of collagenous fibers. Within this necrotic area isolated cysts were seen, lined by ependymal like cells. There was a marked demyelination and partial destruction of nerve fibers with an overgrowth of astrocytes and a formation of dense meshworks of glia fibers. Microscopic Diagnosis: Ependymoma (Figs 20, 21, 22, 23 and 24).



FIG 18—Case 2065 Medulloblastoma (an autopsy material) invading dorsal segment of spinal cord pia arachnoid and outer zone of spinal cord. Van Gieson stain. Zeiss obj 35 oc 16x.



FIG 19—Case 2084 Ependymoma of cerebellum. Sagittal section through brain to demonstrate tumor destroying central part of cerebellum and lined by roof of fourth ventricle.



FIG 20—Case 2084 Ependymoma (autopsy material) Area of necrotic tumor tissue Mild increase in collagenous connective tissue fibers van Gieson stain Zeiss obj 3x oc 6x

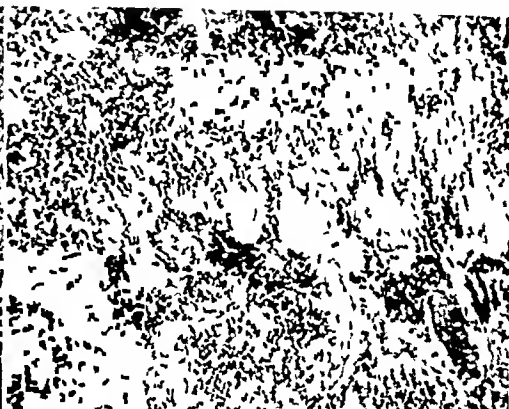


FIG 21—Case 2084 Ependymoma (autopsy material) Island of tumor tissue within area of necrosis H and E stain

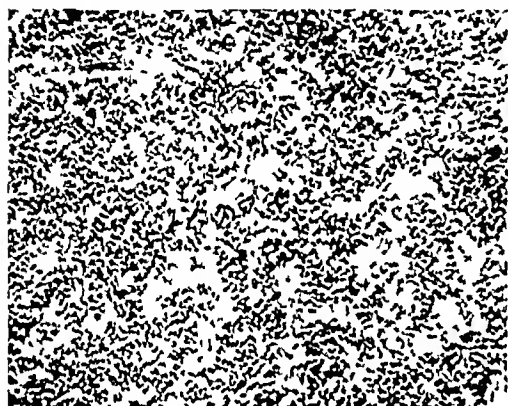


FIG 22—Case 2084 Well preserved tumor tissue in isolated peripheral nodule van Gieson stain Zeiss obj 10x oc 10x



FIG 23—Case 2084 Higher magnification to demonstrate wide unstained areas around blood vessels (showing processes of tumor cells in Davenport stained preparations)



FIG 24—Case 2084 Ependymoma (autopsy material) Proliferation of fibrous glia and argyrophile connective tissue fibers in area of necrosis Davenport stain Zeiss obj 20x, oc 10x

The total amount of deep roentgenotherapy expressed in R units, the duration of symptoms at operation, and the survival period of each patient is shown in Table I. It will be seen that the longest survival period is not necessarily in that patient who received the largest amount of radiation therapy. In fact, one patient with a glioblastoma multiforme survived nine months as compared with a patient with the same type of tumor who survived 16 months but who had received five times the amount of deep roentgenotherapy.

TABLE I
SUMMARY OF DURATION OF SYMPTOMS AND ROENTGENOTHERAPY

Case No	Sex	Age	Duration of Symptoms		Microscopic Diagnosis	Amount of X-ray Treatment
			at Operation	at Autopsy		
2065	M	14	2 mos Survival	12 mos 10 mos	Medulloblastoma	6,000 r units
2084	M	13	6 mos Survival	21 mos 15 mos	Ependymoma	9,100 r units
2098	M	55	3 mos Survival	13 mos 10 mos	Glioblastoma multiforme	6,600 r units
2170	M	48	5 mos Survival	14 mos 9 mos	Glioblastoma multiforme	2,400 r units
2070	M	33	3 yrs Survival	4 yrs 16 mos	Glioblastoma multiforme	12,000 r units
2085	M	27	4 yrs Survival	5 yrs 18 mos	Glioblastoma multiforme	9,200 r units

In summarizing the results histopathologically, it may be said that in four cases of glioblastoma multiforme which had been treated with deep roentgen ray following operation, the central area of necrosis was more extensive and overgrowth of collagenous connective tissue was more abundant than in two untreated control cases. The growth of the glioma in the periphery of the treated tumors had not been arrested. A study of a larger series of such tumors should decide the question whether the difference in the age of the tumors of the treated and untreated cases determined the difference in the histologic pictures or whether it was produced by roentgenotherapy. An ependymoma of the fourth ventricle was markedly inhibited in its growth and only in the periphery of the tumor were well preserved nodules of ependymoma tissue observed. A medulloblastoma of the fourth ventricle was not inhibited in its growth by roentgenotherapy. Extensive invasion of the spinal cord occurred despite prolonged radiation of the skull and spinal column.

From a careful follow up study of our own patients with intracranial gliomata who have been operated upon, it is obvious that there is no evidence that roentgenotherapy has decisively prolonged the survival period beyond the average of those patients with histologically similar tumors who have not received such therapy. Our results are in practical agreement with those reports in the literature in which accurate comparisons have been made

between treated and untreated cases. For example, in Cushing's series of patients with astrocytomata who were treated by deep roentgenotherapy, the survival period was 78 months, as compared with a survival period of 68 months in untreated cases.

Deery¹ studied 50 gliomata in an effort to determine the effect of radiation therapy. He chose only those cases in which both preradiation and post-radiation specimens of the tumors were available, and the majority of the series consisted of medulloblastomata, glioblastomata, and astrocytomata, the three most common tumors in any series of gliomata. Some of the tumors of each type showed very striking histopathologic changes which it seemed reasonable to Deery to credit to the radiation given. Others showed less marked changes, while others showed no demonstrable change whatever. The primary effects of radiation therapy were upon the tumor cells and there were evidences of cell injury which, when severe, resulted in death of the cells. There was an increase of necrosis and a reduction in cellularity of the growth which could be determined by actual cell counts. Mitotic figures were less frequent following radiation and often postradiation specimens showed the appearance of or an increase in giant cell forms. In Deery's opinion the blood vessel and connective tissue phenomena which were commonly seen in postradiation material were secondary and incidental changes. In agreement with our own results, the changes which were apparently caused by radiation therapy were encountered not only in tumors of a lower order of differentiation, which theoretically should be more radiosensitive, but also in tumors of a high degree of maturity such as the astrocytomata.

Alpers and Pancoast² studied 22 gliomata treated by radiation therapy. Only two of six cases of glioblastoma multiforme showed slight hyperchromatosis and fragmentation of the nuclei but no effects which might be considered as lasting. In the medulloblastomata, a change in the blood vessels, necrosis of cells and increase in the connective tissue stroma were noted but there was evidently a lack of correlation between the amount of tumor cell change and the amount of radiation. These authors concluded from their study that although mild changes are produced by radiation, they are not of great importance and suggested that a much greater dose of radiation therapy be used than is now commonly the practice.

Sachs, Rubinstein and Arneson³ reviewed the results of roentgenotherapy in a series of 119 gliomata and as a criterion of the results obtained, stated that, if after receiving radiation therapy, the patient had definite subsidence of symptoms which were still present after operation, it was considered that some beneficial effect had resulted from the therapy. It will be immediately recognized that the personal factor enters into such an analysis which can lead to no uniform conclusions from a study of the problem from several clinics. In general, however, they concluded that radiation therapy has definite inhibitory but only a temporary influence upon glioblastomata. To obtain the best results from radiation therapy of medulloblastomata they believe that radical operative removal must precede treatment, which has a definite effect

on this type of tumor. These authors did not correlate their clinical results with histopathologic studies of pre- and postradiation specimens.

It is at present agreed that surgery and radiation therapy should be used in conjunction and that no antagonism should exist between them. Roentgen or radium therapy without surgery may carry with it many dangers. In the first place, without surgical verification one cannot be certain that a tumor is present. Secondly, there may be a mistake in localization of the lesion. In the third place, several types of intracranial tumors, as has already been mentioned, are not only radioresistant but offer favorable surgical results. Finally, edema and increase of brain volume which follow radiation therapy, may cause an increase in headaches and papilledema. Beclere⁴ has designated these symptoms as a pre-reaction which may occur within half an hour after radiation. He states that vessels dilate, there is hyperemia and a serous transudate and edema occur. Numerous cases are upon record in which a single treatment of roentgen ray has been followed by coma and death and therefore, it must not be assumed that radiation therapy is devoid of danger.

At present, there are no standards of technic of therapy which are universally used. Hyslop and Lenz⁵ have shown by ionization measurements of the effective dosages at possible sites of deep-seated gliomata, that roentgen ray therapy with intermediate or low voltage is inferior to high voltage therapy. They also state that if intermediate voltage therapy is used, one-third of the surface dose may be absorbed by the skull whereas much less radiation is absorbed by the skull if high voltage therapy is used. Sosman's technic, as described in 1928, and practiced upon Cushing's large series of intracranial tumors, consisted essentially of an interrupterless 12-inch transformer with mechanical rectification, 130 to 140 K V peak and a 9 to 10 inch spark gap between blunt points. A filter of 0.25 Mm of rolled copper with one thickness of sole leather was employed on the side next to the patient, with an occasional substitution of a 5.0 Mm aluminum filter. A distance of 12 inches from the center of the target, a milliamperage of 6 and a time interval of 25 minutes for a full dose was used. The portals of entry were 8 to 15 cm in diameter and were delimited by leaded rubber on the patient's head and by lead diaphragms $\frac{1}{4}$ inch thick. The single portal single séance method was used in postoperative cases with a trial dosage of 60 to 80 per cent the first day. A full dosage was repeated every three weeks for from four to eight treatments. Another series of four treatments was given after three to six months. This treatment produced epilation and only occasionally a faint erythema in ten to 14 days. Sosman judged that a single full dose was approximately equivalent to 800-1,000 r units.

Our own method of treatment has been to give a slightly smaller number of R units through four portals of entry. We have used 200 kilovolts with 1 Mm filters of copper and aluminum. The target distance has been 50 cm and the portal size 100 sq cm. The attempt has been made to deliver 125 per cent of an erythema dose to the center of the skull, distributed over four sances 24 hours apart. About 400 to 500 r units are delivered at each

seance This series is repeated after six to eight week intervals for two or more series of treatments After a six to eight month interval, another series of four treatments is given

Recent developments in our knowledge of radium therapy have established certain fundamental principles that have an important bearing upon treatment Thus, it has become recognized that an optimum time interval exists during which a tumor reacts best to radiation Exposure of the growth during a shorter period results in failure to gain a maximum lethal effect upon the tumor cells Exposure over a long period results in the establishment of a state of radio-immunity The importance of utilizing the most penetrating rays of radium has led to the use of adequate filtration, and a recognition of the significance of homogeneous distribution of radiation has resulted in the use of external radiation whenever possible and multiple implants when interstitial irradiation is indicated

Since these principles have become recognized, it is not difficult to explain many of the failures of radium therapy under the older technic The use of glass radon seeds, for example, invariably resulted in necrosis on account of the absence of filtration and the frequent failures of gold implants can be explained on the basis of inadequate filtration and the difficulty of effecting a uniform distribution of radiation except in lesions of limited size

These considerations have resulted in important changes in technic in recent years The ideal form of radium therapy is that which permits the delivery of an adequate, uniform dose of penetrating irradiation over a prolonged but limited interval, for example, by the use of a large quantity of radium at a distance In the treatment of the more radioresistant tumors, however, the amount of radiation that can be delivered to the lesion by external radiation may be inadequate and interstitial radiation becomes necessary in order to deliver an adequate dose to the tumor Under these circumstances the use of multiple weak radium foci adequately filtered and uniformly distributed becomes the method of choice With a few isolated exceptions removable platinum iridium needles of 0.5 Mm wall thickness, containing radium element, have proved to be superior to any other method of interstitial radiation The radium element is distributed throughout the platinum needles in such amounts that the total dose determined by clinical experience is delivered over a prolonged period of approximately five to seven days This distribution of radium permits the use of a small quantity of radium over a period of 120 to 168 hours rather than the use of a larger quantity over a period of 10 or 12 hours In the treatment of cancer of the tongue, for example, the use of this method has proved to be highly successful Within the last few years the use of removable platinum radium needles has been extended to the treatment of other neoplasms, notably in inoperable carcinoma of the breast

Although radium implantation has been practiced in tumors of the brain and numerous studies have been made upon the effect of radium on normal brain tissue, most of these observations were conducted before the basic

principles already described were fully recognized and the radiation was not executed according to the newer technic which recognizes and embodies the factors mentioned

Davis and Cutler⁶ have recently reported upon a series of experiments upon animals and one clinical case in which these newer technical methods were employed. In one series of animals, a 1 mg needle of radium was introduced into the brain and allowed to remain from 24 to 216 hours, at the end of which intervals the animals were sacrificed. In another series, 4 mg of radium were implanted for periods of from 48 to 216 hours, so that the total number of milligram hours were from 192 to 864. After the radium needles were removed these animals were allowed to live and were sacrificed at intervals of two to 168 days. The pathologic studies of the brains of these experimental animals showed a small amount of thickening of the endothelium of the vessels and fat loaded microglia cells in the immediate vicinity of the needle wound but no changes occurred which could not be explained equally as well by the introduction of a needle which did not contain radium. In any event, the destruction of normal nerve cells did not extend beyond a few millimeters from the immediate track of the needle. The one clinical experience was in a glioblastoma multiforme. A radium exposure of 2,688 mg hr was given from needles implanted directly into the tumor and removed at a second operation. The patient died two months later but this case proved to be a severe test of the practicability of the method of interstitial radiation and has encouraged an extension of the method.

In an effort to gain comparative knowledge of the clinical results which follow radium therapy upon intracranial tumors, we have thus far treated 14 patients. In this group there were 5 glioblastomata, 2 astrocytomata, 2 angiomas, 2 metastatic carcinomata, 1 sarcoma, 1 medulloblastoma, and 1 metastatic hypernephroma.

Wherever possible cross-fire radiation was instituted over two areas of the skull. Each patient received 2,000 mg hours each day until a total of 80,000 mg hours through each of the two portals had been given. This made a total of 160,000 mg hours for each patient. Using a 2 Gm radium pack, a distance of 10 cm, a round portal 10 cm in diameter and a 1 Mm filter of platinum was employed. The only variation in this technic using the 4 Gm pack was to employ an 8 by 10 cm portal. Soon, a clinical impression was gained that several of these patients progressed more satisfactorily than a similar group treated by deep roentgenotherapy or left untreated. Unfortunately, when this impression was subjected to rigid analysis against our records it became obvious that no such difference existed between the results obtained by radium and deep roentgenotherapy. The survival periods have been similar in cases which might be fairly compared. As yet, we do not have pathologic material for comparison before and after radium therapy and, consequently, the most authoritative source of arriving at a conclusion must await a future study. Clinically, at least, there would seem to be no choice between the two methods of therapy.

Finally, in summary, it is fair to state that the results of deep roentgen and radium therapy upon intracranial gliomata which have been verified at operation have not been promising and, in fact, have been somewhat of a disappointment. This, in spite of newer methods of technic developed in the therapeutic use of these agents. Any attempt to study the results obtained by radiation therapy should involve a careful histopathologic study of the tumor before and after radiation, and an accurate comparison of the survival periods of these patients.

It must be remembered that certain tumors of the glioma group, by their nature, have a long history before operation and a long survival period. This makes it difficult to evaluate accurately the postoperative effect of either of these two agents. Certain it is that gliomata should be verified surgically before they are treated by deep roentgen or radium therapy.

The story of the surgical treatment of gliomata of the brain has not been completely written and it is likely that future experimental and clinical work will point to a more satisfactory method of dealing with these tumors than is now recognized. In such studies the possibility of deep roentgen and radium therapy by means not yet utilized should play an important rôle.

REFERENCES

- ¹ Deery, E. M. Remarks on the Effects of Roentgen Therapy upon the Gliomas. *Bull Neurol Inst*, New York, 4, 572, 1936.
- ² Alpers, B. J., and Pancoast, H. K. Effect of Irradiation on Normal and Neoplastic Brain Tissue. *Am Jour Cancer*, 17, 7, 1935.
- ³ Sachs, E., Rubinstein, J. E., and Arneson, A. N. Results of Roentgen Treatment of Series of 119 Gliomas. *Arch Neurol and Psychiat*, 35, 597, 1936.
- ⁴ Beclere, A. La radiotherapie des tumeurs de l'encephale. *Paris med*, 47, 97, 1923.
- ⁵ Hyslop, G. H., and Lenz, M. Radiation Treatment of Gliomas of the Brain. *Am Jour Med Sci*, 176, 42, 1928.
- ⁶ Davis, L., and Cutler, M. An Experimental and Clinical Study of the Effects of Radium upon the Brain. *Surg Gynec, and Obst*, 56, 280, 1933.

DISCUSSION—DR ELLIOTT C. CUTLER (Boston) Today, when Mr. Keynes presented so succinctly the influence of radiation upon tumors, the thought occurred to me to again impress upon the profession that radiation therapy may also be extremely useful in the field of neurologic surgery. If I understood Doctor Davis correctly, he feels that one cannot assay, even by survival studies, the beneficial effects of radiation therapy, and feels there must be histologic controls of the effect produced by radiation.

In cooperation with Doctor Sosman, Head of the Roentgenologic Department at the Brigham Hospital, Boston, we carefully studied the postoperative survival period of 61 patients with cerebellar medulloblastomata, and in that group it was clearly indicated that as surgery became better, the survival period was extended from one month to one year, but that with radiation in addition the survival period was greatly extended.

The medulloblastoma like the lymphoblastoma, is a so-called radiosensitive tumor and can seed itself down in the cerebrospinal fluid axis so that metastases occur in the spinal cord region and even upwards in the ventricular apparatus. When radiation is applied to all of the ventricular system one should prevent seeding of the medulloblastoma or kill off the implants, so the survival period

can be extended. This has occurred, and there are now several patients living over six years since their first surgical biopsies were obtained.

The idea that a tumor of this type is particularly radiosensitive has been borne out by the studies of Biody and Geiman at New Haven and by Elsberg of New York. It is very clear now from a study of it, taking biopsies originally, and with subsequent recurrences, that profound effects (at least in our experience) are exhibited in the specimens removed. The tumor shrinks in size, the blood vessels diminish in caliber, and one sees evidence microscopically of considerable alteration in the cell appearances. Certainly in this small field of the medulloblastomata of childhood one can say that radiation has extended life from less than one year to an expected period of perhaps around three or four years. This may be even further extended. The longest known postoperative survival patient in this group is now alive ten years since the first surgical procedure. The second longest survival is alive and well seven years since the first surgical procedure but continues to show spinal recurrence from time to time, the symptoms of which disappear with roentgenotherapy.

I think we should recall today, in discussing radiation as a whole, that there may be tumors of greatly shifting radiosensitivity, but we can find groups of tumors corresponding to a definite cell type which we can predict, if we know the type of tumor, will be radiosensitive even in the field of neurologic surgery.

DR GILBERT HORRAX (Boston). My experience with the medulloblastomata has been exactly the same as that experienced by Doctor Cutler, and I do not believe that Doctor Davis would differ with this essentially, from the clinical standpoint. He simply mentioned one or two instances in which there was no evidence of microscopic change after roentgenotherapy. I think it has become an established fact that medulloblastomata do respond to radiation very definitely, and life expectancy is greater with it than without it. As a matter of fact medulloblastomata strictly speaking, are not tumors of the glioma group. So far as the glioblastomata, the astrocytomata and the oligodendrogliomata are concerned, which are the true gliomata, my experience has been similar to that of Doctor Davis.

I had occasion to look up some 50 of these tumors a year or two ago, which had been verified at operation, subsequently radiated, and then re-operated upon or came to autopsy. These tumors were studied very carefully by Dr Percival Bailey and myself from the histopathologic standpoint, specimens taken at operation being studied through innumerable sections, and the ones taken at subsequent operations studied the same way. We could not convince ourselves that there was any difference whatever in the general character of these tumors after radiation. Likewise, one might say the same thing about the expected survival period of patients with these tumors, because that has become pretty well established now thanks to Doctor Cushing's book on the large series of cases in this group and others, so that we know in a general way what to expect in the survival period of patients with tumors which have been operated upon either with or without radiation.

In looking over these records and going over the sections very carefully, we could make out no difference in the tumors of the distinctly glioma group, that is the glioblastomata, the astrocytomata and the oligodendrogliomata. There was no example of ependymoma in this series so we were unable to judge what might have been the effect of radiation upon them.

DR FREDERICK L REICHERT (San Francisco). I happened to attend the meeting of the American Neurological Association in Atlantic City last eve-

ning, and this question of deep radiation therapy to gliomata was considered. There was quite a lively discussion. The results at the Neurological Institute and with Doctor Sachs in St. Louis seemed very favorable, as after removal of the tumor, they give a massive dose of deep therapy to the bed of the tumor through the open wound. Also, our results with medulloblastomata have been very remarkable with deep therapy, one over six years and four over four years, are alive and well, so that we feel this is the most favorable type of glioma for radiation.

Recently, because of the work done in thermocoagulation of the brain, producing complete destruction of cells, we have applied heat through a radio knife to the bed of the tumor, and with our finger have estimated that the temperature has been very high and that we have destroyed perhaps 2 or 3 cm. beyond the bed of the tumor. In these cases there has been no deep therapy given at all, and although the results are not conclusive, it seems a rather promising method.

DR. LOYAL DAVIS (Chicago) closing: It is very difficult to compare the results of a series of intracranial tumors operated upon some years ago with a similar series operated upon more recently. In the first place, it is freely admitted that the surgical procedures were not as complete and thorough then as now. In the second place, the type of roentgenotherapy was quite different and no method was available for measuring the amount of deep roentgen ray treatment received. In the third place, the pathologic types of tumors were not as well studied as they are at present. For all of these reasons I feel that Doctor Cutler's statement that many cases have done extremely well with roentgenotherapy in the past years is not one which can be taken as accurately as I think this problem should be studied. I would not want to leave the impression that in my own series we have not noted clinical improvement after roentgenotherapy. As I pointed out, this improvement was noted particularly in the cases of medulloblastomata, but we have also seen it in many cases of glioblastomata and astrocytomata. But, and this is the important point, we have seen a similar improvement in the same type of tumor in patients who have had no roentgenotherapy. Doctor Horrax confirmed this point in his discussion.

If one wishes to quote statistics from a large series of patients in which any comparison has been made in the survival period following operation between those who have received deep roentgenotherapy and those who have not, Doctor Cushing's series is the most valuable. He showed, with regard to astrocytomata, a survival period of 78 months in the treated cases and 68 months in the untreated cases—a difference of only ten months, which most of us believe can be explained by the cell type of tumor and particular characteristics of these tumors.

Finally, the point I wish to emphasize is that we must maintain a scientific attitude toward the problem of radiation therapy in intracranial gliomata. We must require the same criteria as are required in a physiologic experiment. We must know as accurately as possible how much of the tumor has been removed surgically. We must know accurately the histologic character of the tumor before roentgenotherapy. We must know the exact amount of radiation therapy given, and we must make an effort to study the brain or any remaining tumor after radiation therapy has been given. Such cases must be compared accurately with cases in which the tumor has a similar cell type but in which no radiation therapy has been given. Only after these exacting conditions have been fulfilled and correlated with the clinical course will we be able to state accurately and definitely the effect of radiation therapy upon the gliomata. In closing, I may say that these same requirements should be fulfilled in all tumors subjected to radiation therapy wherever they be located.

THE PLACE OF RADIUM IN THE TREATMENT OF CANCER OF THE BREAST

GEOFFREY KEYNES, M D CAMB , F R C S ENG

LONDON, ENGLAND

It is now nearly fifty years since your great countryman, William Stewart Halsted, introduced the radical operation for the treatment of cancer of the breast. The technic of the operation has undergone modifications during that period, but Halsted's principle has been accepted throughout the world of surgery, and for many years the radical operation has been more or less standardized. Moreover, the degree of standardization has been some indication of the satisfaction with which surgeons have regarded the results that have been achieved. The satisfaction has been only relative, because treatment of cancer in all parts of the body has been disappointing. The treatment of cancer in the breast has perhaps been less disappointing than in most other situations.

Standardization must not, however, be allowed to lead to an hypnotizing of surgical opinion into a fixed belief that no further improvement is possible and that any suggested change is, necessarily, to be regarded with a cold disapproval. Most surgeons who have taken the trouble to follow up their patients after performing the radical operation for cancer of the breast are, indeed, gravely dissatisfied with their results. I am sure, therefore, that the surgeons here present, representing, I believe, the most advanced body of surgical opinion in the United States of America, will give a sympathetic hearing to an account of an honest attempt to find out whether irradiation with interstitial radium needles might be used to mitigate, or possibly abolish, the necessity for so formidable a procedure as the radical operation. Encouragement is to be obtained from a survey of the present treatment of cancer in general, for irradiation has virtually supplanted surgical operation in cancer of the tongue, mouth and fauces, and in cancer of the cervix uteri. At one time there was a widespread belief that cancer of the breast was not a radiosensitive neoplasm, and it was stated, particularly in some clinics on the continent of Europe, that satisfactory irradiation of the contents of the axilla was impossible. The validity of these statements will be criticized during the course of my remarks, and the final test will be provided when the late results of irradiation are presented to you.

From the ordinary surgical standpoint it is exceedingly unorthodox to suggest that conservative methods of treatment, sometimes without any removal of tissue whatever, could possibly be better than radical operation, or even as good. Previously, I myself maintained that the earlier the disease the more radical should the operation be, since the hope of curing the disease was greater, and I was aghast when some of the older surgeons

such as the late Sir Anthony Bowlby of my own hospital of St Bartholomew's, stated their belief that the patients would do just as well if only a local removal of the breast were effected. I must confess that my opinion has now gone to the opposite extreme, and I am prepared to maintain that, if the axillary lymph nodes are extensively involved, dissection of the axilla may be harmful, and that, if they do not appear to be involved at all, it is unnecessary. This opinion is coupled with the assumption that radical irradiation will be carried out in every case. I have also to confess that I have had increasing difficulty in accepting the theory of centrifugal permeation by cancer cells as enunciated thirty years ago by W. Sampson Handley, since so many of his conclusions seemed to be contrary to experience and contrary to common sense. I have been greatly interested therefore in anatomic investigations on lymphatics carried out recently at St Bartholomew's Hospital by J. H. Gray under the inspiration of Woollard.¹ By the use of thorotrast and barium, lymphatics have been made visible and their course traced more accurately than before, and it has been shown that there is no lymphatic plexus in the deep fascial layers. Thus the lymphatic

system of the breast lies in the gland and on its surface, the main lymphatic trunks passing around the fold of the axilla to the axillary nodes. No evidence whatever has been discovered in support of the theory of centrifugal permeation. On the other hand normal lymphatic channels are found to connect a carcinoma with involved nodes, the only possible inference being that carcinoma cells pass to the nodes as emboli, without forming intermediate points of growth. The supposedly permeated channels have been shown to be generally infiltration in planes of tissue cleavage, or sometimes to be growth in a venule. It

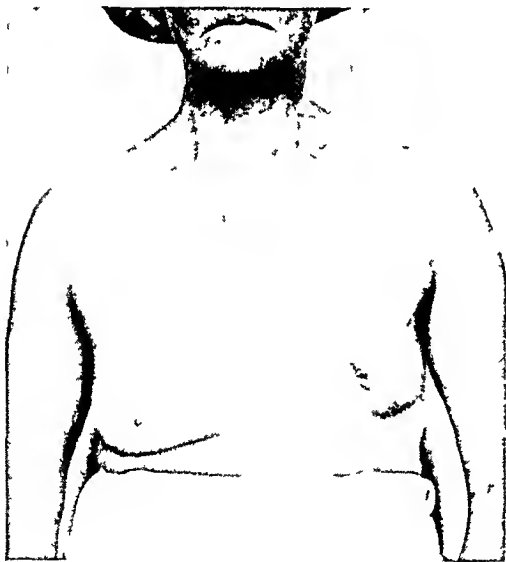


FIG. 1.—Case 1. Ten years after treatment.

follows, therefore, that widespread operations based upon the permeation theory of fascial planes have no real justification. If Gray's observations are correct it will be necessary to revise our conception of the spread of cancer, and then perhaps the idea of conservative treatment of cancer of the breast may become more acceptable to us.

It was first suggested to me by Professor George Gask, in 1922, that an attempt should be made to treat cancer of the breast with interstitial radium alone. For the first two years only patients with recurrent disease following operation were treated. In nearly every instance the growth was observed

to disappear, and the treatment was then extended to the primary disease, the first patients being treated on August 1, 1924. For the next four and one-half years only patients with very advanced or inoperable tumors were treated in this way, and the results in 50 of these were examined before it was thought justifiable to extend the treatment to the earlier stages of the disease. It was soon apparent that the belief that cancer cells in the breast were not sensitive to irradiation must be abandoned. Some remarkable results were obtained, and, although the majority of these patients are now dead from metastases, many of them remained, for periods up to eight years, without external signs of disease. Six of them are now alive nearly ten years after treatment, and five of these six—that is, 10 per cent of the whole—are without signs of disease.

ILLUSTRATIVE CASE REPORTS

Case 1—A patient, age 40, presented herself with a large tumor in her left breast which had already produced elevation of the breast and retraction of the nipple. The



FIG 2—Case 2. Nine years after treatment.

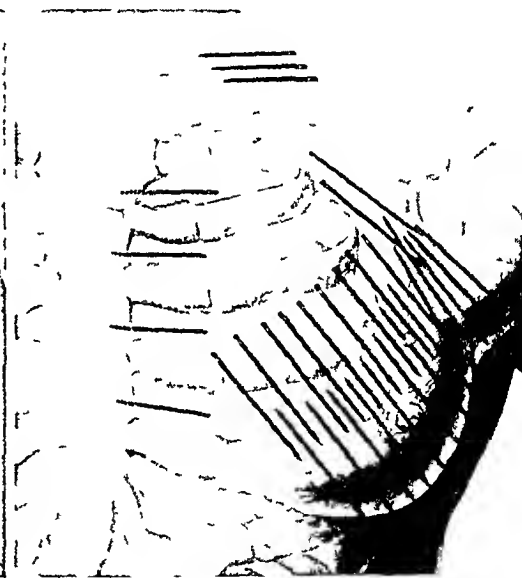


FIG 3—Usual distribution of radium needles.

disease was advanced, though still operable. There were palpable lymph nodes in the axilla. She was treated with radium alone, after the diagnosis had been proved by biopsy. There was some contraction of the breast, which followed the disappearance of the tumor, but the patient is without signs of disease 10¼ years after treatment (Fig 1).

Case 2—A stout patient, age 57, had a very large tumor in the left breast. It was infiltrating the skin and was adherent to the chest wall, so that it was judged inoperable. No secondary metastases in the axilla could be detected, but she was so stout that even large nodes might have been present. She was treated with radium only, and except for a depressed scar in the position of the tumor, she shows no trace of her disease nine years later (Fig 2).

It was perhaps this initial investigation that gave rise to the legend that I was now and forever a convinced irradiator of cancer of the breast and

had completely abandoned surgery in this disease. Undoubtedly I was encouraged to proceed in this direction, I think with justification, but my general surgical bias has, I hope, prevented me from becoming unbalanced. The results will presently be put before you.

When this series of 50 trials of interstitial irradiation had been completed, it was felt to be justifiable to extend the method of treatment to earlier stages of the disease, and from that time to this I have systematically used radium either by itself or in combination with very conservative surgery. The radium has always been applied interstitially in the form of needles. The usual distribution of needles is shown in Fig. 3.

No radon has been used. Surgical operation, if used at all, has preceded irradiation, and has been performed with the diathermy needle. No dissection of the axilla has ever been carried out. These have been the general principles, and I am not concerned today with details of technique.²

The patients were carefully observed, and in due course a certain number of failures were noted. These failures were either shown by incomplete disappearance of the primary tumor or by the appearance of recurrent nodules in the breast or in the skin. In a number of patients these residual tumors were removed and examined nine months or more after the irradiation. It was then found that in 50 per cent of them there was no discoverable cancer remaining, the tumor consisting entirely of fibrous tissue. In the other 50 per cent evidence of active cancer was found. This result led to a reconsideration of the procedure, and it was realized that the failures might reasonably be attributed to the physical limitations of radium needles. The penetrating power of the rays is strictly limited, and many of the tumors were too thick and bulky for the gamma rays to penetrate them effectively from below, so that the cancer cells in the center or at the surface did not receive a lethal dose. Another more theoretic difficulty was the supposed variation in the sensitivity of the cancer cells themselves. I do not attach much importance to the second consideration, but the bulk of the tissue to be irradiated did seem to be a serious obstacle unless the dosage of radium was to be greatly increased, and to this there were other objections. I, therefore, decided to remove more frequently either the tumor or the breast before irradiation, according to circumstances. Sometimes in the earliest stages of the disease it was desirable to remove the tumor in order to establish the diagnosis. Whenever an operation was performed it was as conservative as circumstances would allow, and never included the removal of the pectoral muscles or dissection of the axilla. In the majority of patients, therefore, the amount of mutilation was negligible, and in some, radium only was still employed without any operation at all. This procedure could only be justified if it was evident that the action of radium on the axillary lymph nodes was effective. It may be stated, at once, that close observation of the patients over many years has shown that the results on the axillary nodes have been uniformly good. They have been made

to disappear almost with certainty, and they have not recurred. If the axilla did not contain palpable nodes none have developed afterwards. These facts have crystallized the procedure at the present time as follows:

- (1) Local removal of the tumor if it is large, or the diagnosis is uncertain, followed by radium
- (2) Local removal of the breast if the tumor is very bulky, followed by radium
- (3) Never dissect the axilla
- (4) Radium by itself may be used (a) If the tumor is of moderate size and the diagnosis certain (b) If the patient refuses operation

If the disease has extended to the supraclavicular nodes when the patient is first seen, this has usually been found to be accompanied by disease within the thorax, so that the patient will often be unsuitable for treatment by radium, which, like surgical operation, is essentially a local form of treatment. Apart from the obvious necessity of often rejecting those who showed evidence of metastases in viscera or skeleton, there has been no selection of patients.

In citing statistics I wish to emphasize again the fact that interstitial radium treatment is strictly comparable with surgical operation, in that it is a local form of treatment, although it can be extended to the area above the clavicle which is not usually included in an operation. For this reason no striking improvement in the survival rate was to be expected if radium was used as an alternative to surgery. It is the metastases, and not the primary disease, that usually cause the death of the patient, and for that reason I never shared the exaggerated hopes that were at one time placed by some people in the future of radium. On the other hand, some local advantages were to be expected if the general results seemed to justify its use. The patients have been divided into three groups:

Group I Disease apparently confined to breast

Group II Disease apparently confined to breast and axilla

Group III Disease advanced or inoperable

The statistical results have been prepared for me by Lady Janet Forber who has done a great deal of similar work in compiling cancer statistics for the Ministry of Health. They may be relied upon for their accuracy. Finally, please remember that I am a general surgeon on the Staff of a large teaching hospital, so that I have no special cancer or breast clinic, and the number of patients treated by me, even in the course of ten years, is not large.

The total number of patients treated up to the end of March, 1937, is 325. Of these, those treated within the last three years must be excluded from the statistics. This leaves 250 as the total available for statistical examination. These are distributed as follows among the groups: Group I, 85; Group II, 91; Group III, 74.

The percentage survival rates among these 250 patients have been ascertained by Lady Forber (Table I)

TABLE I
PERCENTAGE OF PATIENTS ALIVE AFTER THREE YEARS

Group	Number	Survival Percentage	U C H * Survival Percentage
I	85	83.5	79.2
II	91	51.2	52.3
III	74	31.4	—

PERCENTAGE OF PATIENTS ALIVE AFTER FIVE YEARS

I	75	71.4	69.1
II	66	29.3	30.5
III	60	23.6	—

* In the fourth column I have added the survival rates obtained as the result of a recent investigation carried out at University College Hospital,³ as this seemed to be the nearest approximation that I could obtain to a comparable series of a similar number of patients treated by surgery alone

The only category of really curable patients is that included in Group I, and this is, therefore, the most interesting to us as clinicians. You will agree that survival rates of 83.5 per cent and 71.4 per cent at three and five years are satisfactory. The University College Hospital series gave 79.2 per cent and 69.1 per cent for the same periods, and probably it is fair to assume that in round figures 80 per cent and 70 per cent may be regarded as average results with the best surgery. My figures for radium are slightly above this average. I should attach no importance to this slight difference were it not for the fact that the statistics in this group are weighted heavily against me. When Group I relates to the results obtained by the radical operation, the contents of the axilla have been removed and examined histologically, so that those patients having involved nodes which were not clinically palpable have been eliminated. My Group I, on the other hand, is necessarily a clinical group only. There can be no doubt that a proportion of them would prove to have involved nodes if the contents of the axilla were examined. My Group I is therefore composed, in reality, of a mixture of Group I and Group II patients, and is, therefore, more unfavorable than would appear at the first glance. Lady Forber informs me that there is no material for forming an accurate basis upon which to correct this error in grouping. Such material as there is indicates that the possible error is in the neighborhood of 27 per cent. She has applied this correction to my series, and she then finds that my corrected survival rate for the patients in Group I is 94.8 per cent at three years,

and 86.3 per cent at five years. I must confess that these figures frighten me, and I doubt whether it is wise to publish them in print, as they contain too large an element of conjecture. I think it is fair to assume, however, that my survival rate for true Group I patients would be substantially higher than appears in Table I.

In Group II the survival rates of approximately 51 per cent and 29 per cent at three and five years are almost exactly the same as those obtained from the series at the University College Hospital. In this group so many of the patients are necessarily doomed to die from metastases which have already started when they first come for treatment, that little improvement in the survival rate could be expected.

In Group III, where I obtained a survival rate of approximately 31 per cent and 24 per cent at three and five years, it is impossible to give any comparable figures obtained from the results of surgery, since so many of the patients are judged, wisely enough, to be inoperable. The survival rate that has been obtained among these patients is the more remarkable when it is remembered that they represent those cases which have been considered inoperable, the patients that the surgeon will not look at because he knows he cannot help them, those, in fact, that he willingly allows the radiologist to treat.

I have already mentioned that although none of the patients has been subjected to dissection of the axilla, an increasing number of them have had the tumor, or the breast, removed before the radium treatment was given. Comparatively few of these, however, come into the five or three year periods, so that the number of patients thus treated are too small to be worth computing separately as percentages. So far as they go, the figures suggest that there may be a slight further improvement following the preliminary excision, though this cannot yet be asserted with confidence. There will, however, be a considerable improvement in the incidence of secondary minor operations for local recurrences.

It is perhaps idle to seek at present for any definite cause to which the apparent rise in the survival rate of Group I patients following radium treatment may be due. I can only point out that the radical operation has a definite operative mortality. It is in the neighborhood of 3 per cent according to the University College Hospital statistics. Radium, on the other hand, has practically no operative mortality. Up to the present time only one patient has died while under treatment, and she was found to be suffering from advanced cardiac disease with decompensation, from which she might have died at any moment. This operative mortality would probably militate more against Group II patients suffering from more advanced disease than against Group I. Nevertheless, elimination of this mortality might make a difference of 1 per cent in Group I. The radical operation, undoubtedly, delivers a knock-out blow, from which many patients do not really recover for a considerable time, and it is possible that their "resistance

to the disease" (whatever that may be) is lowered by the shock which they suffer. The shock from interstitial radium, on the other hand, is practically nil, so that here again an advantage may result, though this is theoretical. Finally, there is the complete elimination of surgical interference with the lymphatic system of the axilla. I think it is not impossible that this dissection, as commonly performed, may sometimes disseminate the disease, when it has been temporarily held up in the neighborhood of the axillary lymph nodes.

Interstitial radium, on the other hand, irradiates cancer cells in that situation without disturbing them, and this may possibly be a real factor in obtaining a better survival rate. Again this is theoretical, and I am sure that more knowledge must be obtained concerning the exact mechanism of the dissemination of cancer before the matter can be settled to our satisfaction. I make the above suggestion, however, particularly in view of the results obtained with radium in Group I, and in view of the work of Gray and Woollard, which they think points to dissemination being largely the result of embolism. They even deprecate, on this basis, any more handling or squeezing of a cancerous breast than is absolutely necessary. I have often wondered in past years, as I watched patients being examined by twenty or thirty students in succession, whether this might not be seriously affecting their expectation of life, and now it seems as if the answer may be in the affirmative. Gray and Woollard are of the opinion that my suggested explanation of the improvement in Group I with radium is probably correct.

I have assured you already that I do not speak with any antisurgical bias, since pure surgery is the chief preoccupation of my life. Yet I feel that it must be the ambition of every conscientious surgeon to help in the gradual elimination of any operative procedure so extensive and severe as the radical operation for cancer of the breast. I cannot help, therefore, being interested in noting what may be achieved apart from statistics by the conservative method I have described in comparison with radical surgery. No one can deny that radical surgery entails, in addition to an appreciable operative mortality, a really hideous mutilation. There is, as a rule, remarkably little limitation of strength and movement of the arm, unless the interference with the axilla results (as it not infrequently does) in an obstruction of the lymphatics of the arm, with its attendant swelling and helplessness. This sequela, when it occurs, is very distressing indeed. Again, routine radical surgery does apparently sometimes result in actual dissemination of the disease and widespread recurrences in the skin flaps and their surroundings. It is impossible to escape the conclusion that radical surgery does sometimes do more harm than good. Finally, and, I believe, very importantly, there is the psychologic aspect. Most women know what is meant by surgical treatment of cancer of the breast, and I am sure that very often they are intimidated by the prospect. As surgeons we con-

stantly regret the fact that patients do not come to us soon enough, very often hiding their disease until two years or more have elapsed since it was first noticed. I am afraid it is the fact that we *are* surgeons that is partly responsible for this attitude on the part of the patients. They are afraid of us, and, frankly, I am not surprised that they should be. It is this feeling that deters them from seeking advice, and so prevents any considerable improvement in the end-results such as might follow earlier diagnosis and earlier treatment in the aggregate.

Let me now refer to the advantages and disadvantages of conservative treatment such as I have outlined. The mutilation is usually slight, and very often may truthfully be called negligible. A distinguished lady came to me three years ago for treatment of cancer of the breast, and to this



FIG 4—Case 1 Six years after treatment

FIG 5—Case 2 Six years after treatment

day her husband—who was abroad at the time—does not know that she has ever been ill.

CASES ILLUSTRATIVE OF RESULTS OF CONSERVATIVE TREATMENT

Case 1—B, age 38, had a nodule of growth in the axillary tail of the right breast. It was excised with diathermy, and radium treatment given in August, 1931. She is without signs of disease nearly six years later (Fig 4).

Case 2—W, age 38, gave a similar history. The lump was excised, and she was given radium treatment only. She is also without signs of disease nearly six years later. There has been some contraction as the result of the treatment, and the breast is somewhat elevated in comparison with the other (Fig 5).

Case 3—C, age 34, was treated recently by excision of a nodule of cancer in the right breast, and then by radium. Eight months later the breast is practically normal (Fig 6).

Case 4—C, age 61, who had a small tumor in the upper part of the left breast. The treatment was the same as in Case 3, and eight months later the breast is apparently normal (Fig 7)

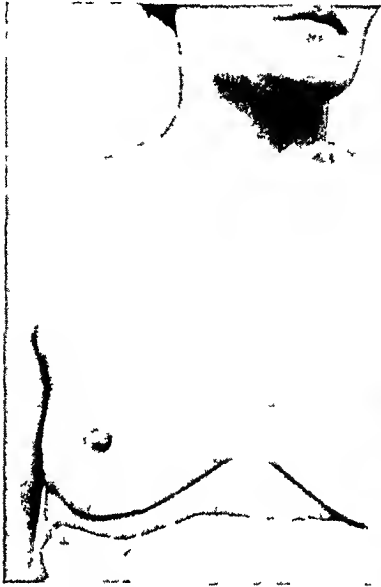


FIG 6—Case 3 Eight months after treatment



FIG 7—Case 6 Eight months after treatment

There can be no doubt of the esthetic advantages of conservative treatment

Case 5—W, age 39, when first seen, had a very early carcinoma in the outer part of the right breast. This was treated by excision for diagnosis, followed by radium to the outer half of the breast only. Remained well for nearly five years, and then

showed signs of a second carcinoma in center of same breast with deviation of nipple. Patient refused operation, and was treated with radium only. Eighteen months later a very small nodule in the left breast, which had been under observation for some time, became larger and there was a blood-stained discharge from the nipple. This nodule was excised and proved to be a third carcinoma, and radium was applied to the breast. The patient now shows some contraction of the right breast which has had two treatments, but is otherwise quite well, over eight years after being first treated (Fig 8). She would rather have died than have submitted to removal of a breast, and is unique in my series in having had treatment for three primary growths apparently with success.



FIG 8—Case 5 Eight years after first treatment

With conservative methods there is, as I have said, practically no operative mortality, and there is never any operative shock. I have never seen lymphatic edema of the arm which was due to radium. If it occurred it was always due to extension of the disease into the upper part of the thorax. Widespread, local recurrences after radium treatment are very uncommon, and they do not even appear to be attributable to the treatment. Finally a number of patients have been encouraged to undergo treatment only because they were to be spared the mutilation entailed by surgery. Patients have sometimes said, and written to me, most moving things in this connection, and I have no doubt that if conservative treatment were to be commonly practiced, it would finally have the result of bringing more patients to the benefits of early treatment, and so improve the end-results.

Against these advantages of conservative treatment I must (if I am to be honest) set certain disadvantages. There is, for example, the difficulty of the interpretation of results. I have already mentioned the possibility of there being a residual tumor after treatment by radium alone, and the difficulty of knowing whether this contains active carcinoma or not. In addition to this there is the postirradiation fibrosis which is apt to appear, as long as two years after treatment, in the positions where the irradiation has been most intense. It is particularly liable to occur on the inner wall of the axilla, and many of my patients have fibrous lumps in that situation which would unquestionably be diagnosed as recurrent cancer by inexperienced observers. Needless excisions of these lumps, and long experience have enabled me to distinguish, confidently, between fibrosis and recurrence, but I can see that they introduce real difficulty in the way of widespread adoption of the method. Eighteen months ago I treated a lady for a very early cancer of the breast, and subsequently she returned to South America. Events then took place which greatly alarmed the surgeons in Brazil and afterwards in Baltimore, though I feel sure, in my own mind, that the patient did not have a recurrence of carcinoma.

Another disadvantage of the conservative method is the increased liability to neuralgia or rheumatic pains in the treated areas. It is true that every woman who has had a cancer of the breast is likely to exaggerate slight pains because she always thinks that pain indicates recurrence. Nevertheless, the treated areas do certainly remain for some time more likely to give rise to pain than an operation scar, and the patients are, to that extent, more conscious of their past experiences. I have never encountered among my patients a true brachial neuritis due to placing needles too close to the brachial nerve trunks. I have seen it produced, however, in another clinic, and it must be remembered that radium needles are dangerous instruments if employed with insufficient skill (but so, also, is a scalpel or almost any of the instruments that we are accustomed to use in surgery). Postirradiation fibrosis may also affect the pectoral muscle and produce some degree of limitation of movement. This is greater when the position of the disease

in the breast or axilla necessitates placing a large dose of radium over and under the border of the pectoral muscle. In treating early disease this is not necessary, and the resulting limitation of movement is negligible.

I have tried to present to you, without too much elaboration, the results of a clinical experiment which has now extended over 14 years, and I venture to suggest that the results show that the experiment has not been a failure. Statistics seem to indicate that a definite improvement can be obtained in the most favorable group of patients by means of the treatment of cancer of the breast that I have used, and the method is therefore worthy of attention. It is conservative treatment rather than purely radiologic treatment, and I think that by combining radiology with surgery we may perhaps get the best of both methods of procedure. I do not wish, however, to make any dogmatic claim on behalf of radium. It may be that the future lies with Professor Coutard.

In conclusion may I express my gratitude to the late Dr. Joseph C. Bloodgood, to Dr. James Ewing, and to many other American surgeons, for the interest they have taken in my work, and for the encouragement they have given me. I must also express to you, my high appreciation of the honor that you have done me in inviting me to take part in this discussion.

REFERENCES

- ¹ St. Barthol. Hosp. Rep., 49, 322, 1936, Brit. Emp. Cancer Camp, 13th Report, p. 34, 1936.
- ² Brit. Journ. Surg., 19, 415, 1932, Acta Radiol. Scandinavica, 10, 393, 1929.
- ³ Lancet, 2, 424, 1936.

INTERSTITIAL RADIATION OF CANCER OF THE BREAST

A REVIEW OF NINETY-SIX CASES OF CANCER OF THE BREAST TREATED
ACCORDING TO THE TECHNIC OF GEOFFREY KEYNES¹

LELAND S MCKITTRICK, M D

BOSTON, MASS

FROM THE PALMER MEMORIAL HOSPITAL, BOSTON, MASS

O'BRIEN¹ quotes the late Sir Berkeley Moynihan as saying that he had not operated upon a cancer of the breast for over a year and doubted that he would ever do so again. Such a statement from so eminent a surgeon could not but profoundly impress the reader. It was undoubtedly stimulated by the excellent work of Mr Geoffrey Keynes, whose first publication² relative to his work in the use of interstitial radiation of primary cancer of the breast had only recently appeared. It was with keen interest, then, that the gift of 1½ Gm of radium to the Palmer Memorial Division of the New England Deaconess Hospital, and the encouragement and cooperation of our former president, Dr Daniel F Jones, and the late Dr Robert B Greenough made possible the study, a report of which is offered at this time.

TABLE I

SYNOPSIS OF THE NINETY-SIX CASES TREATED AND THE MODALITIES EMPLOYED

	Radium Only	Radium and Amputation	Radium and X-ray	X-ray and Radium Primary	Late	Deaths
Operable	10	10	6			1
Inoperable	20		13	8	6	2
Recurrent	10					
Insufficient data to use	13					
Totals	53	10	19	8	6	3

SCOPE OF STUDY—A total of 96 cases have received interstitial radiation at the Palmer Memorial Hospital (Table I). I am privileged to include in this group those cases treated by other members of the staff who have given me access to their records, and their hearty cooperation in the interpretation of results. This limited number of cases, particularly the limited number of primary operable cases is such that the character of our study must be somewhat restricted. It would be impossible to make any contribution in regard to end-results. We do believe, however, that by carefully studying the small group of so-called operable cases and by limiting this study to the direct effect of radium upon the tumor-bearing areas, valuable information may be obtained and certain conclusions may be justified which will have

*I am indebted to Drs G A Leland, Jr, E M Daland, Grantley Taylor and Chas C Lund for permission to include cases treated by them.

considerable bearing upon the value of this method of treatment, particularly in those patients whose general condition makes possible the choice of treatment

We are especially interested in the effect of interstitial radiation, with or without supplementary external radiation, upon the cancer cells in a given breast, in its effect upon such cells in the lymph nodes within reach of surgical dissection, and upon borderline and inoperable cases

DESCRIPTION OF TERMS *Interstitial Radiation*—Interstitial radiation as used in this paper applies to the use of radium element according to the method described by Mr Geoffrey Keynes. A detailed description of the technic will be given later in this paper

Roentgen Ray Treatment—Roentgenotherapy has been subject to some variation during the time that these patients have been treated. In general, primary cases were given a total of 3,000 to 4,500 roentgen units (r) to the breast and axilla through two or three 20 by 20 cm fields using a current of 5 milliamperes at 170–180 kilovolts, a filtration of 0.5 Mm of copper plus 4 Mm of celluloid, at a distance of 50 cm. Patients treated subsequent to the use of interstitial radiation were usually given 1,500 to 3,000 roentgen units. Three to five hundred r units were given daily.

Operable—By an operable cancer of the breast we mean a breast tumor freely movable upon the chest wall, with a sufficiently limited involvement of the skin to permit a wide removal of normal skin and closure of the resulting wound. Lymph nodes, if present, cannot be palpated above the lower part of the axilla, enlarged supraclavicular nodes are absent, and the cancer is not of the so-called inflammatory type. Under these conditions we would expect early and satisfactory healing following radical operation, and except in rare cases, freedom either from local recurrence or from metastases to the axilla dissected.

TECHNIC—For purposes of this work there have been available 78 needles containing radium sulphate as follows. Fifty-eight needles 6.0 cm in length over all with an active length of 4.8 cm, containing 3 mg of the salt filtered with 0.5 Mm of platinum and iridium, 20 needles similarly made 4.4 cm over all, with an active length of 3.2 cm and containing 2 mg of salt. In general from 6 to 12 2 mg needles, and 20 to 40 3 mg needles were used, the total dosage varying from 13,000 to 25,000 mg hours.

Introduction of Needles—In the placing of the needles we have attempted to thoroughly radiate the entire breast with a maximum of radiation delivered to the tumor-bearing area, the axilla, the supra- and infraclavicular areas, and the sternal margin are also radiated. We attempted in our first case to introduce the needles underneath the sternum as advocated by Keynes, but this patient developed considerable emphysema of the subcutaneous tissues around the neck and upper chest. Subsequently, we discontinued this part of the technic, placing instead a 3 mg needle overlying each intercostal space on the affected side, and at least two needles parallel with and overlying the opposite costosternal margin (Figs 1 and 2). Various methods of skin preparations

CANCER OF THE BREAST



Fig. 1

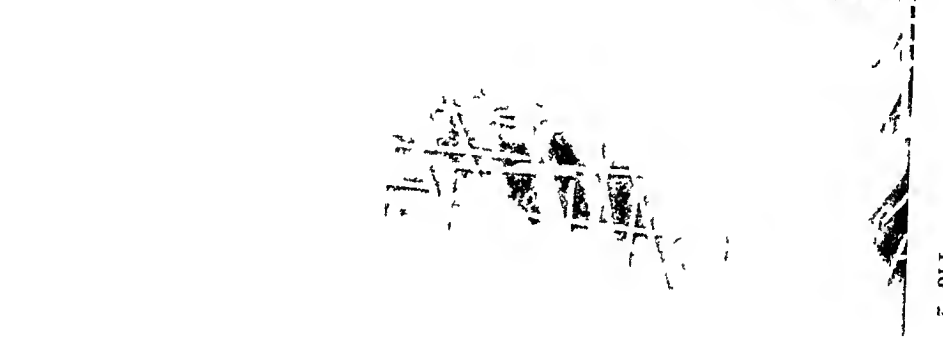


Fig. 2

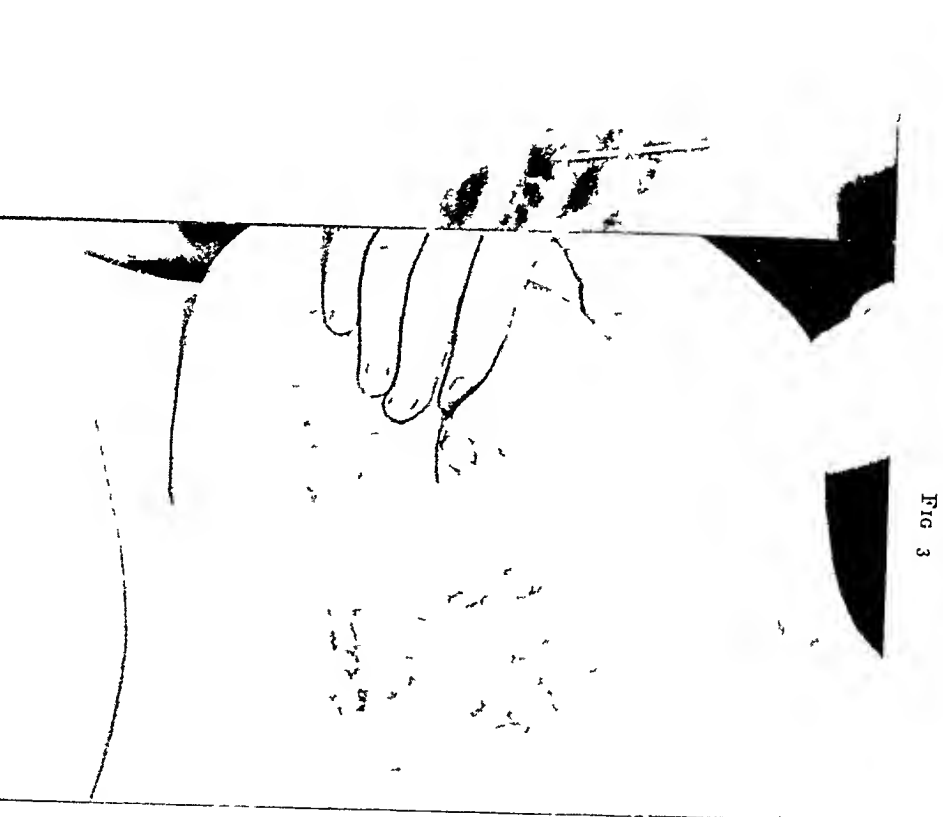


Fig. 3

Fig. 1—Case No. 32621. Showing roentgen needles in place. The dark spot medial to the nipple is a piece of leaded rubber cut the exact size of and overlying the breast tumor (see Fig. 2).

Fig. 2—Same patient as Fig. 1. Roentgenogram showing needles in place. Note needles above and below clavicle, in the axilla, along the opposite margin of the sternum, and the gridiron arrangement in relation to the tumor.

Fig. 3—Same patient as Fig. 1 and 2. Showing roentgen resection. It is brought 21 days after treatment. Thirty seven 3 mg. and nine 2 mg. needles were used over a period of 147 hours, a total of 18943 mg. hours being given. Notice the deep erythema surrounding the area of superficial ulceration in the tumor-bearing area. The mass entirely disappeared and the breast was surprisingly normal to palpation nine months later when the patient died of metastatic cancer of the liver. At autopsy Doctor Warren found "tumor acini lying in dense fibrous tissue." Two of the sections showed cancer.

were used but the one most frequently used by the writer was the painting with tincture of metaphen of a narrow strip of skin, approximately 3 cm in width, along the line of insertion of the needles. The number of needles made available for a given case depended to a large degree upon the size of the breast and tumor to be treated. Needles were threaded with a variety of suture materials, but that found most satisfactory was a No 7½ white braided silk inserted through the needle eye and tied at the end.

In the cases treated by Dr George Adams Leland, Jr, a small incision was made in the axilla, the finger was inserted along the axillary vessels, and the needles inserted into the axilla under direct vision with the axillary vessels protected by the finger. Gas-oxygen anesthesia or, recently, evipal has been preferred by the writer but avertin was the anesthetic of choice by Doctor Leland.

Small punctate incisions were made with a sharp pointed scalpel, approximately 1½ cm apart, two or three of the 2 mg needles were inserted above the clavicle and in the infraclavicular area, a 3 mg needle was inserted over each intercostal space near the sternal margin, and usually two or three needles placed parallel to the opposite sternal edge. Finally, needles were introduced in relation to the tumor. These were first placed deep to and around the periphery of the tumor avoiding, if possible, the insertion of the needles into the tumor itself. It was customary, whenever possible, to insert a second layer of needles superficial to the growth and at right angles to those underneath (Fig 2). With some of the larger tumors it was found necessary to insert the needles into the growth itself. Careful needle count was kept, a firm dressing applied and, except in cases with ulceration, the dressing was untouched until the time for removal of the needles.

Removal of Needles—A short anesthesia was usually necessary for removal of the needles. Early in the series some difficulty was encountered by breaking the thread when tension was applied. This was avoided by sliding the suture through the eye of the needle for one or two centimeters before making any attempt to withdraw it. This is particularly important because of probable damage to the suture at the time of introduction. The end of the needle acts somewhat like the barb on a fish-hook, causing it to catch in the tissues unless the line of pull is the same as the long axis of the needle. Difficulty from this was avoided by first pulling the needle in the direction in which it was inserted before reversing the pull to remove it.

Diagnosis—Guided by Keynes' experience, that in certain cases carcinoma became implanted in the biopsy wound, we did not remove a specimen for pathologic examination in our earlier cases. It was felt that in a well developed cancer of the breast, clinical diagnosis was rarely in error, and this was particularly so if the diagnosis in each instance was confirmed by a second opinion. Therefore, in each case before treatment, the patient was seen either by Doctor Greenough or Doctor Jones, in addition to myself. As a matter of practical importance, however, it so happened that in almost every instance the diagnosis was sooner or later confirmed, either by a pathologic

section or by the clinical course of the disease. The one doubtful case in this series, to be mentioned later, was referred by Doctor Greenough, since there was some uncertainty as to the diagnosis, a biopsy was performed at the time of treatment and was reported as chronic inflammation, later following amputation of the breast a diagnosis of chronic cystic mastitis was made. Careful and critical review of every other case in the series leads the writer to believe that there is no doubt about the diagnosis in any other case, although in at least one instance it may lack pathologic proof.

It soon became evident, however, that a pathologic diagnosis was of utmost importance and removal of sufficient tissue to make this possible became routine. A small incision was made directly over the tumor after all the needles were in place, and a piece of tumor about 5 cm. in diameter and 1 Mm. in thickness was removed for study, the skin edges were approximated with silk sutures which were removed when the radium was taken out. All wounds healed by first intention and there was no instance of recurrent cancer in the scar. The pathologic examinations in all cases but one were made by Dr. Shields Warren, pathologist of the New England Deaconess Hospital. Case No. 31-845 was examined by Dr. Sidney Dalrymple.

Duration of Treatment—Periods varying from six to ten days were used, but like Keynes we found seven days to be most satisfactory, and this became the routine length of time that the needles were left in place.

CLINICAL COURSE FOLLOWING TREATMENT—(a) *Skin*. A slight beginning erythema was usually present at the time of removal of the needles. This increased until two or three weeks after treatment, when vesiculation and loss of superficial layers of skin over the tumor-bearing area not infrequently appeared (Fig. 3). We were most impressed by the widespread diffuse skin reaction which occurred over the entire breast area, supra- and infraclavicular regions, and along the pectoral margin to the axilla. This we feel justified in interpreting as evidence of fairly intense radiation of the entire breast. This reaction completely subsided within six weeks. Late cases show atrophy and telangiectasis characteristic of radiation reaction in the skin overlying the area of most intense radiation (Fig. 4).



FIG. 4.—Photomicrograph 20074, Case No. 32 725. Showing radiation effect on skin of breast. Note loss of normal contour of skin and of superficial epithelium with absence of basement membrane. Note absence of skin appendages. Note marked ectasia of capillaries and lymphatics of corium together with hyalinization of collagen in lower portion of picture (Warren).

(b) *Tumor* Not infrequently there was some shrinking of the growth at the time of removal of the needles. The speed of regression varied greatly and was dependent more upon the response of the individual tumor to radiation than upon its size. In general, the hard scirrhus tumors of long duration showed least response (Figs 5 and 6). In certain instances there was complete disappearance of the mass within two months. In other cases the tumor became gradually smaller and did not disappear until four or even five months had elapsed. There was a change not only in the size of the mass but also in its consistency. It became softer and in many instances a mass persisted or recurred which was described as being fibrous rather than hard.

After six to eight months the entire breast became edematous, firm, heavy and inelastic. The skin over the dependent area had the typical orange-peel appearance. In several instances the breast gradually became smaller and more or less fixed to the chest wall (Fig 8), although in one of our oldest living cases (5½ yrs) the treated breast is two to three times the size of the normal breast and very heavy. In either case the resulting deformity was equal to that following amputation (*cf* Figs 7, 8, 9).

The most disturbing and most frequently mentioned late after effect of treatment was pain along the free margin of the pectoralis muscle, accompanied by a palpable thickening and partial limitation of abduction of the arm (Figs 9A and 9B). This occurred in spite of any precaution on our part to avoid it and was due to edema and fibrosis in the pectoralis major muscle secondary to radiation.

RESULTS—Operable Cases Twenty-six patients were treated where the lesion might be classed as operable (Table II). Radium was selected as the treatment of choice in these patients because of age, size, or some physical disability which tended to make them poor surgical risks. In two instances, patients in otherwise good condition were treated. (1) Because of enlarged supraclavicular nodes, at first interpreted as being metastatic, but later proving to be tuberculous in nature, (2) because a node in the opposite axilla was misinterpreted as being metastatic. Both of these patients later came to amputation. It is, of course, this group which is most instructive, particularly since ten of the surviving 26 patients were later subjected to amputation of the diseased breast.

TABLE II
PRIMARY OPERABLE TUMORS

Type of Treatment	Degree of Regression			
	No	100%	50% and over	Less than 50%
Radium and amputation	10	5		5
Radium and X-ray	6	3	2	1
Radium only	10 (1 death)	7	1	1
Totals	26	15 = 60%	3 = 12%	7 = 28%

It is of no little significance that 15 or 60 per cent of these tumors suffered complete primary regression, three or 12 per cent diminished by 50 per cent

or more, and only eight or 28 per cent proved to be resistant to radiation to a sufficient degree to be diminished by less than one-half of the original size. In other words, 72 per cent of these cases might be classed as radiosensitive.

TABLE III

FIFTEEN CASES WITH COMPLETE PRIMARY REGRESSION OF TUMOR

	No	Comment
Subsequent amputation	5	1 cystic mastitis 1 radium reaction 3 cancer
Died with recurrent mass	4	3 clinically cancer 1 doubtful
Died without recurrent mass	2	1 metastases to axilla and neck 1 cancer in breast at autopsy
Alive	3	1 5 mos, no mass 1 4½ yrs, ? mass 1 5½ yrs, no mass

It is of interest to follow the local condition in the 15 patients in whom complete primary regression occurred (Table III). This may be briefly summarized as follows. Five of these patients were subsequently operated upon, in three, a definite diagnosis of cancer was possible in the breast removed, in one, there were no cells found which could be interpreted as malignant, but extensive radium reaction was present. This was clinically cancer of the breast, diagnosis being made without qualification by both Dr. D. F. Jones and myself. It lacks pathologic proof, yet I firmly feel that we have every reason to believe that this breast had been sterilized of its cancer by the radium given. The fifth case was reported as cystic mastitis. This was in keeping with the clinical picture. Moreover, a previous biopsy had been reported as chronic inflammation. I do not believe that this patient had cancer. Of the remaining ten patients, four died with a recurrent mass, three of these were clinically characteristic of and, without question, were cancer. The fourth one might well have been inflammatory and definite doubt might be raised as to its nature. Case No. 32-621 (Fig. 2) nine months after treatment without any palpable mass, with a perfectly soft, flexible breast, presented the best clinical result of any patient treated. At autopsy, however, careful examination of the breast showed definite viable cancer cells surrounded by fibrous tissue in two sections of breast tissue. A sixth patient died without a demonstrable mass in the breast but with large metastases to the neck and axilla. Three patients in this group who had not been operated upon are alive, one, five months after treatment has a questionable mass, one, four and one-half years after radiation has recently developed a small sensitive, indefinite mass in relation to the chest wall at the lower margin of the pectoralis major. There is no mass in relation to the original tumor-bearing area. The third patient is alive five and one-half years after treatment, without any external evidence of disease, with a large heavy edematous breast, two to three times the size of the breast on the opposite side. There



FIG. 5.—Case No. 32934. Hard nodular tumor of seven years duration. No palpable axillary nodes. Thirty 3 mg and ten 2 mg needles were left in place for seven days, a total dosage of 1840 mg, hours.

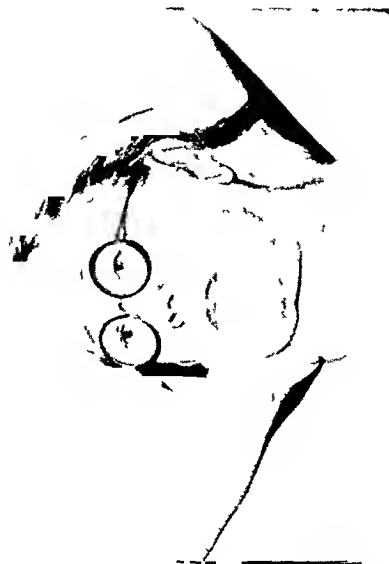


FIG. 6.—Same patient as Fig. 5. Three months later. Superficial ulceration but very little decrease in size of mass.



FIG. 7.—Same patient as Figs. 5 and 6. Four and one half years after radical amputation. No clinical or roentgenologic evidence of disease. The depressed area at the site of the original tumor was caused by necrosis of the underlying costal cartilage and rib.

Fig 8

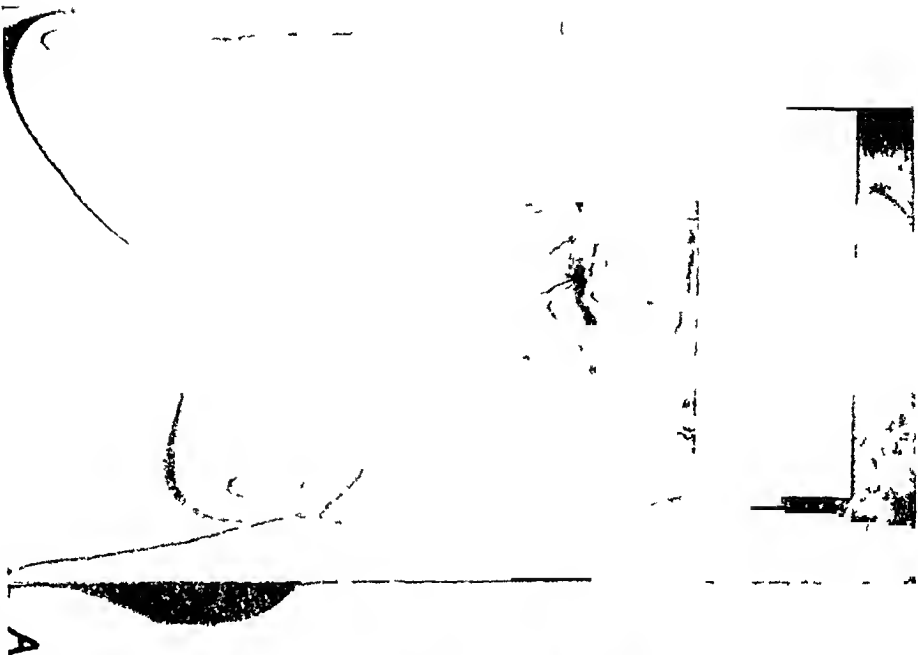


Fig 9

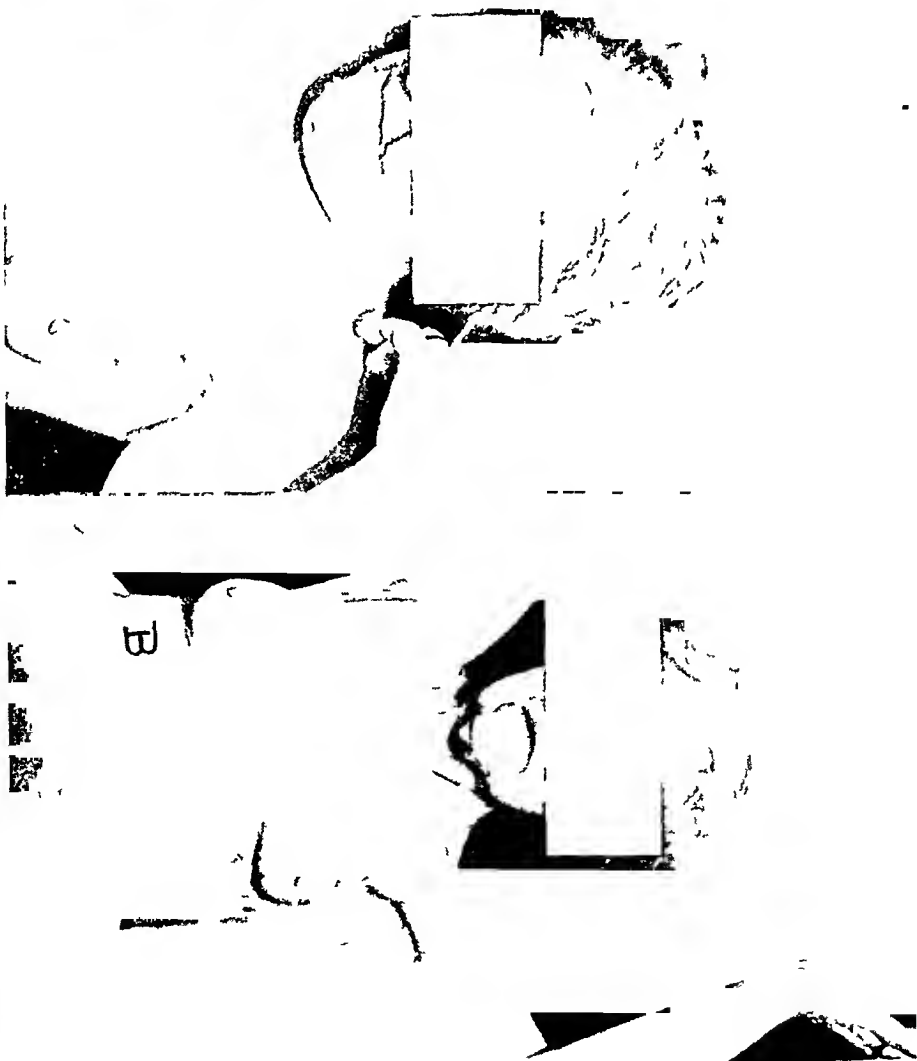


Fig 8—Case No. 32356. Treatment April 28, 1932, thirty-five 3 mg. and four 2 mg. needles for seven days (16,766 mg. hours). Pathologic. Carcinoma simplex. Dec 31, 1934, 800 r units X-ray, Feb 12, 1935, 1,100 r units X-ray. Alive and well May, 1937. Note contour and fixation of breast also atrophy of skin and telangiectases in upper outer quadrant.

Fig 9—Same patient as Fig 8 (A) Three and (B) five years after first treatment. Note thickening and contour of pectoral ridge which has gradually improved through abduction is still markedly limited.

was no mass that I could feel in the breast, although palpation was extremely difficult

It would seem that one might conclude from the above that in a so-called operable breast tumor, interstitial radiation offered an excellent chance of bringing about a complete disappearance of the growth. There would be, however, an almost equal chance that a mass would either persist or reappear and if such did occur it would usually harbor viable cancer cells. It would also seem reasonable to conclude that even though complete disappearance of the mass did take place, the presence of cancer in small foci throughout the breast was not excluded by failure to feel a mass, and that at some future date reappearance locally might be expected to occur, although we can easily understand why such appearance might be postponed for a number of years, due to the fibrosis which has occurred following the course of such intensive radiation.

TABLE IV
RESUME OF TEN CASES IN WHICH AMPUTATION FOLLOWED RADIATION

Hosp No	Age	Treatment Received	Interval between First Radium and Amputation	Indications for Amputation	Pathologic Findings
32-778	64	(1) Radium (2) X-ray (3) Radium	13 mos	Painful tumor, recurrent	Chronic cystic mastitis—marked radium reaction
32-725	64	(1) Radium (2) X-ray (3) Radium	12 mos	Painful mass at pectoral margin, recurrent	Carcinoma simplex in rare foci
34-724	70	Radium	4 mos	Persistent tumor	Carcinoma simplex
32-444	45	Radium	4 mos	Persistent tumor	Adenocarcinoma
31-813	60	(1) Radium (2) X-ray	16 mos	Painful tumor, recurrent	Carcinoma simplex in scar
31-845	58	Radium	12 mos	Persistent tumor	Scirrhus carcinoma, axillary nodes neg
30-1055	70	(1) Radium (2) Radium	21 mos	Persistent tumor	Carcinoma simplex
31-1023	62	(1) Radium (2) X-ray	22 mos	Painful swelling	Radium reaction, abnormal cells probably epithelial
32-934	61	Radium	3 mos	Persistent tumor	Carcinoma simplex Metastases to axilla
35-1089	82	Radium	20 mos	Painful swelling	No demonstrable cancer in breast Metastatic cancer in 5 of 7 axillary nodes*

* Treatment and operation by Dr G A Leland, Jr —axillary application of radium under direct vision

Amputation Following Radiation—This group of ten cases would seem to be of sufficient interest and importance to justify independent discussion. In Table IV are listed the important factors in this group of cases. Certain points are deserving of special note. As pointed out by Keynes, the presence of a tumor does not in itself justify a diagnosis of cancer. Conversely, although the given tumor may be largely inflammatory, this does not exclude the presence of small foci of carcinoma. Thus, Case No. 32 725 was operated upon 12 months after the initial radium treatment. This, however, had been followed by a course of roentgenotherapy and by a second treatment with interstitial radiation. She returned to the hospital with the complaint of a painful mass at the pectoral margin, not, however, at the site of the original tumor. At operation, the mass was found to consist for the most part of inflammatory tissue, but there were definite, though rare, foci of cancer cells found on careful pathologic examination (Fig. 10). On the other hand, Case No. 31-1023, who returned with an area of local swelling and pain 22 months after treatment, was found after operation to be free from any demonstrable evidence of cancer; the mass proved to be entirely inflammatory, the pathology showing only evidences of radium reaction.

It is interesting to note that in five instances operation was precipitated by the presence of a painful tumor. In each instance the mass had suffered complete primary regression. In two of these breasts no cancer was found, one of these undoubtedly being benign at the onset but in three of them cancer was proven pathologically following operation. It is, we believe, this uncertainty as to whether the tumor does or does not contain cancer—an uncertainty existing not only in the mind of the physician but also in the mind of the patient—which is one of the definite disadvantages which this method of treatment presents.

Inoperable Cases—The results obtained in this group of cases are not nearly so striking, nor so instructive, as the group which may be classed as operable (Table V). It is interesting to note, however, that if one classes as radiosensitive those cases in whom the growth has diminished to less than one-half its original size, approximately the same incidence of radiosensitivity



FIG. 10.—Photomicrograph 20074. Case No. 32 725. Cluster of viable tumor cells lying in fairly dense fibrous tissue representing residuum of carcinoma. Radiation reaction indicated by marked fibrosis and by abnormal appearance of numerous fibroblasts (Warren). Treatment: September 14, 1932. Thirty-four 3 mg. and ten 2 mg. needles, seven days (20 538 mg. hours). January, 1933. 1,700 r. units X-ray. April 12, 1933. 16,830 mg. hours interstitial radiation. September 22, 1933. Operation.

is found in this group as in the group of smaller tumors. Complete regression, however, occurs only one-half as frequently as in the smaller group. In many instances, these tumors were very extensive, involving the entire breast and, at times, the overlying skin, and one cannot but be impressed with the tremendous local improvement which these patients as a group enjoy. Most striking, of course, is that group of cases with extensive ulceration such as that shown in Figs 11A, B and 12A, B. This group of cases we believe, however, are most satisfactorily treated by heavy external radiation to the limits of skin tolerance, followed in three to five weeks by interstitial radiation.

TABLE V
PRIMARY INOPERABLE TUMORS

Type of Treatment	No	100%	Degree of Regression	
			50% and over	Less than 50%
Radium only	20 (2 deaths)	6	4	8
Radium and X-ray	13	2	7	4
X-ray and radium	8	4	4	0
Totals	41	12 = 31%	15 = 38%	12 = 31%



FIG 11—Case No. 33771. Showing breast before and six weeks after roentgenotherapy.

The local result in this entire group of cases seems to depend upon the size of the local tumor almost as much as upon its radiosensitivity. The larger and more extensive the tumor, the less likelihood of a completely satisfactory local result, so that it is our impression at this time that if more than one

quadrant of a breast is involved in a malignant process, at least preliminary roentgenotherapy is indicated. If the tumor is radiosensitive and there is a marked diminution in size of the tumor following this treatment, further improvement will in every instance be obtained by radium. In all probability this improvement will exceed that obtained by subsequent external irradiation. This we believe primarily because of our experience in a relatively limited number of cases which had been treated by heavy external radiation until the process had become absolutely stationary, and then been sent to the hospital—three from the Massachusetts General and three from the Huntington Hospital—for interstitial radiation. Each one of the six cases had definite regression following radium, although in no instance was there complete disappearance of the tumor.

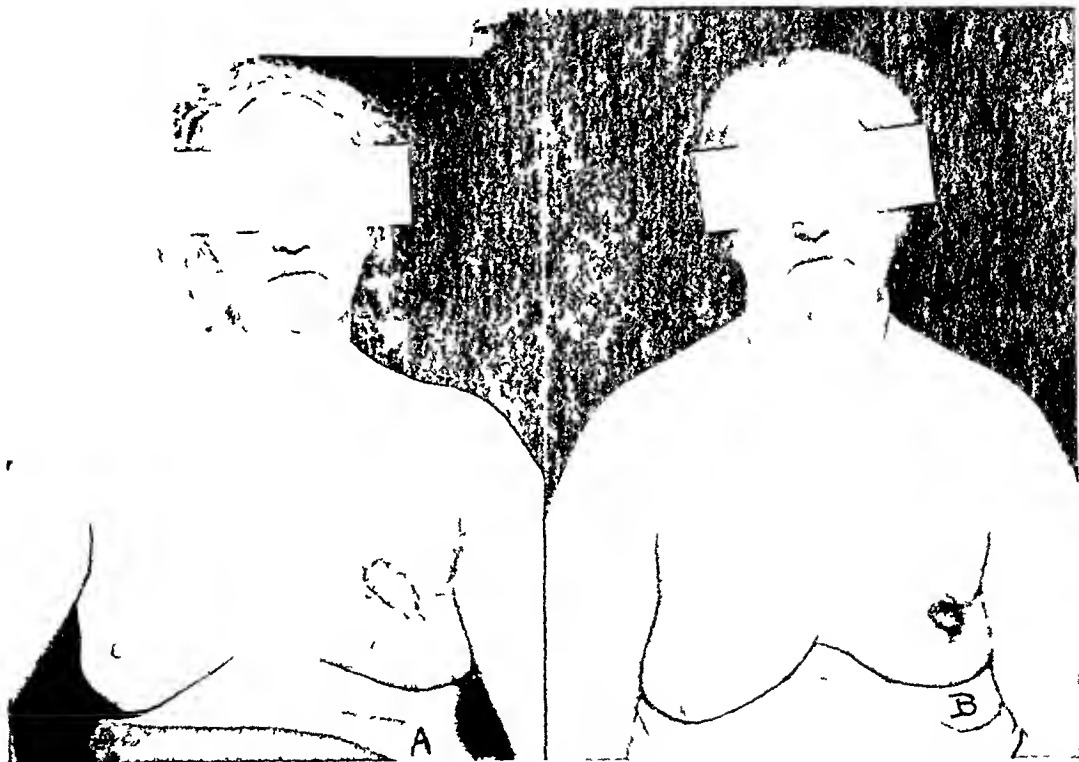


FIG 12—Same patient as Fig 11 (A) Three months after roentgenotherapy and directly after removal of radium (B) Three months after radium treatment. Patient died three months later, nine months after original treatment. The ulceration was dry but not entirely healed.

Recurrent Cases—There were ten cases in this series of local recurrence following amputation of the breast. In each instance satisfactory regression resulted. Our experience, however, would not suggest that the results to be obtained in the smaller multiple local recurrences were sufficiently improved over those obtained from the simpler roentgenotherapy to justify the use of interstitial radiation.

SUMMARY—Ninety-six cases of cancer of the breast were treated at the Palmer Memorial Hospital by interstitial radiation according to a slight modification of the technic described by Keynes.

Twenty-six of these were operable cases. Sixty per cent of these patients

is found in this group as in the group of smaller tumors. Complete regression, however, occurs only one-half as frequently as in the smaller group. In many instances, these tumors were very extensive, involving the entire breast and, at times, the overlying skin, and one cannot but be impressed with the tremendous local improvement which these patients as a group enjoy. Most striking, of course, is that group of cases with extensive ulceration such as that shown in Figs 11A, B and 12A, B. This group of cases we believe, however, are most satisfactorily treated by heavy external radiation to the limits of skin tolerance, followed in three to five weeks by interstitial radiation.

TABLE V
PRIMARY INOPERABLE TUMORS

Type of Treatment	No	Degree of Regression		
		100%	50% and over	Less than 50%
Radium only	20 (2 deaths)	6	4	8
Radium and X-ray	13	2	7	4
X-ray and radium	8	4	4	0
Totals	41	12 = 31%	15 = 38%	12 = 31%

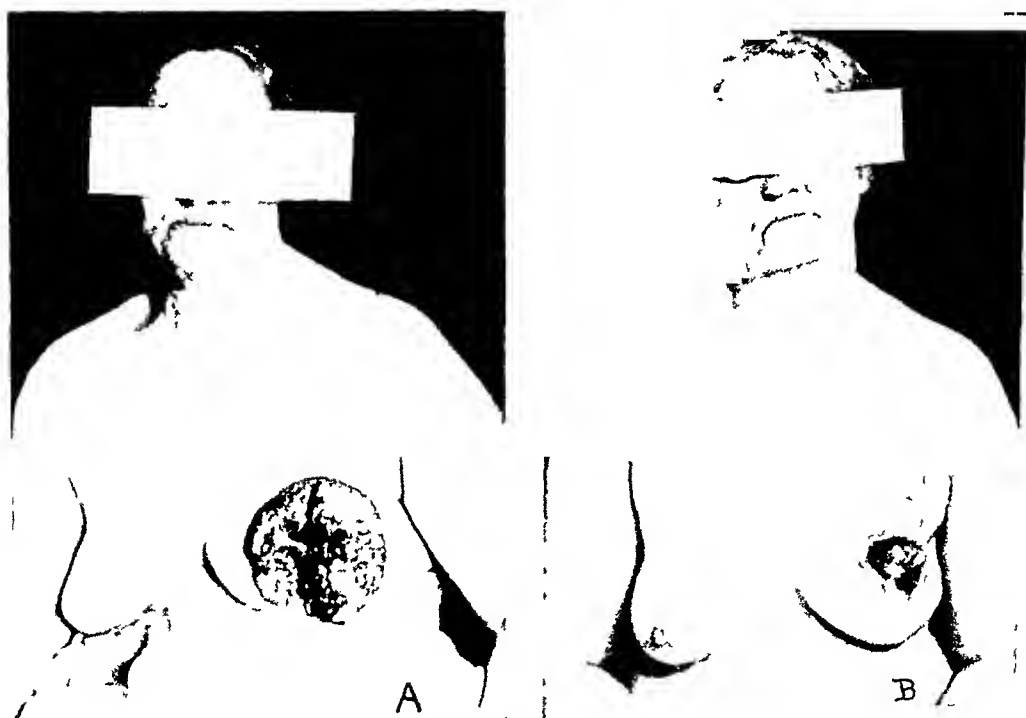


FIG 11—Case No. 33771. Showing breast before and six weeks after roentgenotherapy.

The local result in this entire group of cases seems to depend upon the size of the local tumor almost as much as upon its radiosensitivity. The larger and more extensive the tumor, the less likelihood of a completely satisfactory local result, so that it is our impression at this time that if more than one

quadrant of a breast is involved in a malignant process, at least preliminary roentgenotherapy is indicated. If the tumor is radiosensitive and there is a marked diminution in size of the tumor following this treatment, further improvement will in every instance be obtained by radium. In all probability this improvement will exceed that obtained by subsequent external irradiation. This we believe primarily because of our experience in a relatively limited number of cases which had been treated by heavy external radiation until the process had become absolutely stationary, and then been sent to the hospital—three from the Massachusetts General and three from the Huntington Hospital—for interstitial radiation. Each one of the six cases had definite regression following radium, although in no instance was there complete disappearance of the tumor.

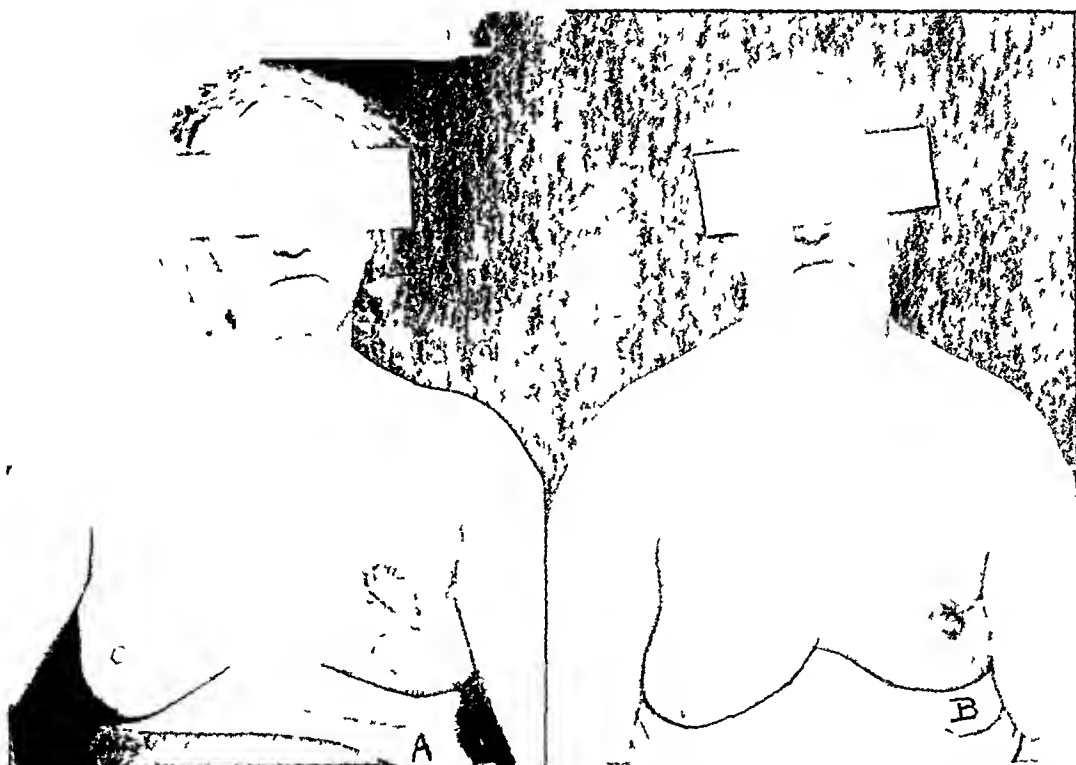


FIG 12—Same patient as Fig 11 (A) Three months after roentgenotherapy and directly after removal of radium (B) Three months after radium treatment. Patient died three months later, nine months after original treatment. The ulceration was dry but not entirely healed.

Recurrent Cases—There were ten cases in this series of local recurrence following amputation of the breast. In each instance satisfactory regression resulted. Our experience, however, would not suggest that the results to be obtained in the smaller multiple local recurrences were sufficiently improved over those obtained from the simpler roentgenotherapy to justify the use of interstitial radiation.

SUMMARY—Ninety-six cases of cancer of the breast were treated at the Palmer Memorial Hospital by interstitial radiation according to a slight modification of the technic described by Keynes.

Twenty-six of these were operable cases. Sixty per cent of these patients

had complete primary regression of the growth and in an additional 12 per cent the tumor diminished in size by more than one-half

A recurrent mass frequently develops which may be cancer or may be inflammatory. It may or may not contain viable cancer cells and represents a distinct mental hazard to the patient.

Viable cancer cells were demonstrated at autopsy in a breast free from any palpable abnormality.

CONCLUSIONS

Having ever in mind the limited experience which so small a series permits, it would seem justifiable to conclude that

(1) Interstitial radiation is an efficient and practical method of radiating a breast cancer.

(2) It probably offers a better chance of sterilizing a given breast of its cancer than does roentgenotherapy as carried out up to the present time.

(3) The finding of viable cancer cells in surgical and autopsy specimens, the pain in, and fixation of the pectoral ridge and the late deformity of the breast after radiation, represent hazards which in our minds render this form of treatment less desirable than surgery in cases of primary operable cancer of the breast.

(4) In an inoperable cancer of the breast where the tumor occupies no more than one quadrant of the breast it may be the treatment of choice.

(5) Large inoperable ulcerating tumors and rapidly growing tumors of the inflammatory type which have shown satisfactory regression following roentgenotherapy will receive greater benefit from interstitial radiation given three to five weeks after the roentgen ray than from subsequent external radiation.

(6) It has no advantage over roentgen ray in the management of large massive lesions or in lesions which have shown little response to adequate roentgenotherapy.

(7) It cannot be depended upon to protect the axilla against metastatic invasion.

REFERENCES

- ¹ O'Brien, F W. Irradiation of Primary Cancer of the Breast. *New Eng Jour Med*, 202, 897, 1930.
- ² Keynes, Geoffrey. The Treatment of Primary Carcinoma of the Breast with Radium. *Acta Radiol*, 10, 393, 1929.

THE TREATMENT OF SOME ABDOMINAL CANCERS BY IRRADIATION THROUGH THE OPEN ABDOMEN COMBINED WITH CAUTERY EXCISION

LEO ELOESSER, M.D

SAN FRANCISCO, CALIF

FROM THE DIVISION OF SURGERY, STANFORD UNIVERSITY MEDICAL SCHOOL AT THE SAN FRANCISCO HOSPITAL

OUR efforts at treatment of deep-seated or bulky cancers by roentgenotherapy have been checked partly by the damage done by the rays to healthy tissues, and partly by peculiar qualities of the roentgen rays themselves. Ideal for treatment would be an evenly penetrating, utterly selective ray, one of even efficacy from the beginning to the end of its path, one which destroys tumor, but leaves healthy structures unaffected—an ideal to be striven for, but apparently unattainable. The next best thing would be to use such rays as we have at our disposal, but to get all vulnerable, presumably healthy structures out of their path and to irradiate only the cancer itself and the areas invaded or likely to be invaded by it. Fulfillment of this postulate would at the same time obviate considerably the need for making compromises in the quality of the ray chosen from the roentgen spectrum for treatment. The practice of deep radiotherapy has led us, hitherto, to choose, not soft unfiltered rays, which have the most destructive surface effect, but hard, copper-filtered ones, of less intensity. The reason for this paradoxical choice lies in the absorbability of the soft ray, a large part of which is lost in the surface layers of the tissue which it traverses. The rays which pass through a copper filter are less intense, if not less active biologically, however, they penetrate the tissues further and more evenly. If, therefore, an adequate percentage of the surface dose is to reach a deep-seated growth, hard rays need to be chosen, for soft ones will be absorbed in the intervening tissues, so that but a small fraction of the surface dose will reach the growth.

Chaoul has recently perfected a method whereby he reduces his focal distance greatly and works through a small port. The method is applicable to superficial tumors of not too great bulk. Irradiation is confined to the tumor itself, the surrounding tissues are affected only for a short distance. This limitation is a serious disadvantage in the treatment of diffusely invasive growths.

A method which would exclude healthy tissues from irradiation and which would bring the tumor itself and the presumably invaded areas into as close and as direct contact as possible with the source of radiation, would have many advantages. Exclusion of healthy vulnerable tissue is highly desirable. Irradiation of resistant tissues, connective tissue, muscle, fascia seems not to matter much, irradiation of the skin to the point of weeping desquamation is by no means negligible, far more important, and the chief stumbling-block to adequate irradiation of intra-abdominal cancer, has been the extreme sensibility of the mucosa of the small bowel. The lining of the

small bowel seems considerably more sensitive than the lining of the stomach or the colon, it is more sensitive than the skin. Epilatory doses may destroy the whole mucosa from the pylorus to the ileocecal valve and lead to death in four or five days. A *sine qua non* for efficient abdominal radiotherapy would be to remove the small bowel from harm's way.

These ideas are not new. Methods based upon these considerations were tried during the early days of roentgenotherapy. They seem to have been abandoned after more even penetration of the ray was secured by diminishing its intensity by means of copper filters. Approximation of the involved area to the source of energy and exclusion of bulky masses which absorb the ray would lessen the amount of copper filtration necessary to secure adequate penetration of the cancerous area itself and increase the amount of radiation available in a given time. It would thus shorten the exposure necessary for saturation of the field, which, other things being equal, is an advantage, for prolonged exposures are uncomfortable, distressing, and under certain circumstances harmful.

These are advantages of the method about to be described that admit of little doubt.

The method as applied to most intra-abdominal cancers has the disadvantage of admitting of but one heavy, a very heavy exposure, rather than a series of fractional exposures, the value of which Professor Coutard has so firmly established and upheld against controversy. It may be that smaller supplementary fractional doses and deep irradiation, administered later through the skin in the usual manner, may be of value, they have not yet been tried. Such a plan would approximate Pfahler's modification of Coutard's method. The initial heavy dose would be delivered directly to the tumor, subsequent smaller doses designed to maintain saturation would have to be delivered through the skin and small bowel, but could be made small enough to avoid damage.

The method to be described has been used for cancers of the colon, the rectum and the stomach the extent of which either precluded any attempt at removal, or made cure after such an attempt seem highly improbable.

One of the barbiturates, usually sodium amytal, is given one hour and morphine one-half hour before operation. The abdomen is opened, under spinal anesthesia, through a long incision, which permits of easy exposure. If the patient is apprehensive or restless, evipal or avertin may be used in addition. The abdomen is explored in the usual manner to determine the feasibility of removing the cancer and the presence of lymphatic or distant intraperitoneal metastases, the liver is palpated. The growth is then removed if it seems anatomically possible to remove all palpably cancerous tissue. Dissection and excision are carried out, not with the endotherm, but with the heavy Percy galvanocautery. Excision having been completed, the abdominal wall is held open with a self-retaining retractor, the small bowel is packed off with gauze and the skin protected with pieces of sheet lead cut to the required shape. The lead is folded over the edges of the wound, so

that it and the gauze packing hold the small intestine out of the way, the lead at the same time shielding the small bowel from irradiation (Fig 1) In this way a large cylinder, with a diameter of some five inches, is held wide open, the suspicious area from which the cancer was removed lies at the bottom of the cylinder The patient is then irradiated, some 2,500 to 4,500 r being administered unfiltered, through variable thicknesses of aluminum, or through 0.25 to 0.5 Mm of copper Filtration varies with the thickness and mass of suspicious tissue to be treated The tube is placed as close as possible to the mouth of the incision, usually at a focal distance of 30 cm Its close approximation to the cancerous area not only shortens the time of exposure but increases the field of radiation When exposure is complete, the packing and the lead protective strips are removed and the abdominal wound is closed

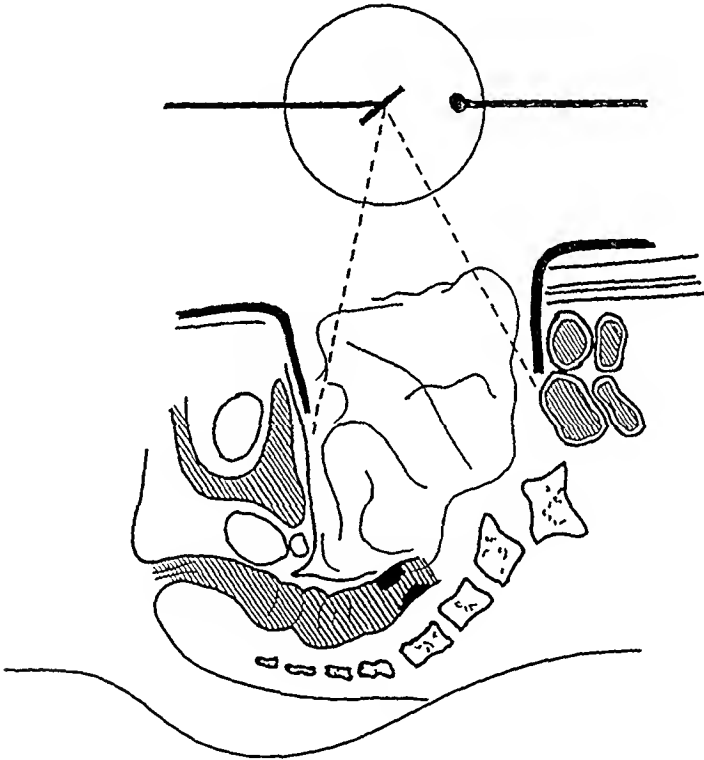


FIG 1—Irradiation of cancer of sigmoid (abdominal approach)

Cancers of the sigmoid, high cancers of the rectum, cancers of the ascending colon are easy to prepare for treatment by this method Exposure is simple and it is not difficult to induce an even anesthesia without nausea, during which the small bowel may be kept out of the pelvis by gauze packs and protected by lead shields It is equally easy to protect the bladder With the bladder, the small bowel and the anterior abdominal wall shielded and out of the way, nothing remains the irradiation of which need cause concern, except possibly the skin of the sacral region Some patients have had a mild erythema of the sacral skin, however, the posterior part of the pelvis itself filters off a large part of the rays Lower cancers of the rectum, invasive cancers of the cervix and cancers of the bladder and prostate would

also lend themselves to this form of treatment, should it prove of value. They could be irradiated as described, from above, or they could be irradiated from below, lead protection if necessary being introduced from above via a laparotomy incision (Fig 2), or from below via the opening into the Douglas pouch.

Cancers of the stomach and of the upper abdomen are more difficult to isolate for roentgen treatment. It would probably be wise to shield the pancreas and the third portion of the duodenum in cancers of the stomach without retroperitoneal lymphatic metastases. This would mean opening the omental bursa and inserting sheet lead into the retrogastric space. Two apparently hopeless cancers of the stomach, one resected, the other not, were treated without thus protecting the pancreas. In both of them, although there was no other evidence of disturbance of pancreatic function, intractable nausea and anorexia followed.

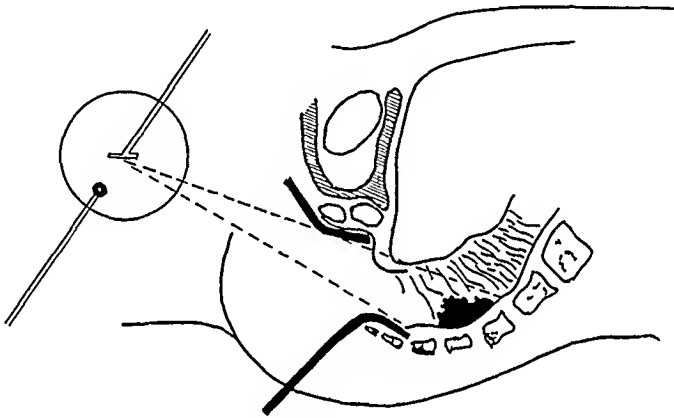


FIG 2—Irradiation of cancer of rectum (perineal approach)

Whether to irradiate before or after removal of the growth has seemed doubtful. Murphy was able to so affect a field by irradiation, so that viable cancer implanted into it failed to grow. If these experiments are applicable to human cancer, then irradiation should logically precede excision, this scheme has been followed in superficial cancers—the breast, head, neck, *etc*. In abdominal cancer it seemed advisable to perform excision first, it seemed wise to remove a bulky mass, so that a softer ray might be used for treatment of what cancer might remain spread out along the fascial planes. It also seemed advisable to undertake excision first, so that, if for any reason it seemed wiser to cut short the operation, the cancer at least would have been removed.

The high single doses up to 4,500 r were given in the face of protest from the radiologist, who felt sure that severe diarrhea would result from exposure of the sigmoid or high rectum and feared damage to the bladder, should it happen to project into the field. However, nothing happened, the bladder mucosa did not exfoliate, there were no disturbances of the bladder and usually no diarrhea from the colostomy opening or discharge from the anal stump. The colostomy opening was subsequently closed and the de-

ascending colon united to the anal stump in several patients. In one patient recently operated upon, a high rectal cancer was not removed, the bowel was adherent to the pelvic wall and there were hepatic metastases. This patient has some diarrhea, but the stools are not bloody and the rectal mucosa, as seen through the proctoscope, is scarcely changed.

The series in which the method was tried is small. It was used only in patients with cancers so large or so widespread that recovery by ordinary means seemed impossible or highly unlikely. Results seem to warrant further trial. Variation and further extension of the method suggest themselves. Thus, some breast cancers have been irradiated through the open wound, which during operation seemed to have extensions leading to inaccessible areas, *e g*, extension leading into the thorax along the humero-intercostal nerve bundles, furthermore, a few cancers of the neck and pharynx, in which it seemed desirable to protect the skin and the larynx. The equipment at hand was clumsy and inefficient. It is hoped that a better installation will be available.

CASE REPORTS

Case 1—Adenocarcinoma of the Colon with Lymphatic Metastases, Recurrent Six Months After Removal in the Form of a Fungating Growth Invading the Lateral Abdominal Wall and Retrocolonic Space. S. M. S., a diabetic, age 67, was referred by Dr. Chas. D. Fletcher on January 7, 1933. Three brothers and a sister had died of cancer of the intestinal tract. A mass could be felt on the left side of the abdomen. At operation, January 12, 1933, a thickened and dilated loop of small bowel was found tightly adherent to a carcinomatous mass, originating in the descending colon. No distant metastases were demonstrable. The small bowel was resected and united end-to-end, the descending colon was isolated with the Percy cautery and some seven inches of it were resected. The stumps of the colon were left open in the form of a colostomy. The resected colon contained multiple diverticula, numerous papillary polypi and an ulcerated, infiltrating carcinoma, the size of a hazelnut, which had invaded the musculature of the bowel wall. Sections of the tumor showed an invasive adenocarcinoma, section of the adjacent lymph nodes also showed metastatic carcinomatous involvement.

The growth recurred promptly. During July, 1933, a fungating mass appeared in the colostomy wound which on microscopic examination proved to be a carcinoma. It was determined to attempt to remove this recurrence, because the tumor mass, although attached to the abdominal wall, was itself movable and no distant metastases could be demonstrated. Accordingly, on July 13, 1931, under spinal anesthesia aided by gas, the skin around the colostomy stoma was incised elliptically and closed over the colostomy opening. Adhesions between the omentum and the bowel were separated with the Percy cautery. The distal segment was freed, severed between clamps and the infiltrated mesocolon approached. The proximal end of the colon, including several inches above the tumor, was also freed with the cautery and severed between clamps, after which the whole tumor mass, including the colostomy stoma and some of the musculature of the lateral abdominal wall, which appeared invaded, was removed with the cautery, leaving a wound bed which to the naked eye seemed free of tumor. A piece of sheet lead was bent into the form of a tube, having a caliber of about three inches, this was pointed toward the retroperitoneal space and the lateral abdominal wall, protecting the small bowel. 1,600 r were administered through 0.5 Mm. of copper under the direction of Dr. Lloyd Bryan. The upper and lower ends of the colon were then brought out in the form of a colostomy. Recovery was uneventful. There was no nausea, on July 18 and 19 there was a mild diarrhea with mucous stools. On July 20 the stool was again formed.

Pathologic Examination—The section was reported by Dr David A Wood as showing extensive invasion of the muscularis by a proliferating tumor mass, the latter possessing a reticulum of moderate thickness enclosing spaces lined by short columnar epithelium and forming atypical irregular glands. The tumor cells were hyperchromatic and showed occasional mitosis. *Diagnosis* Recurrent carcinoma of the colon.

The patient has been reexamined frequently since and has shown no signs of recurrence. It seemed most unlikely that this carcinoma should not recur after a second removal as it had after the first, unless something more than mere surgical extirpation was undertaken. The family history, the lymphatic metastases and especially the invasion of the abdominal wall by this promptly recurring, fungating growth made the outlook most unfavorable.

Case 2—Adenocarcinoma of Sigmoid with Attachment to the Parietal Peritoneum. M R, age 39, was seen in 1930 with bleeding from the bowel, the source of which was never determined. He appeared again in June, 1936, with symptoms of low intestinal obstruction. Exploration, June 12, 1936, revealed a constricting growth of the sigmoid attached to the peritoneum at the side of the bladder. There was some ascites, but no other evidence of intraperitoneal metastases, no lymphatic enlargements and no hepatic metastases were demonstrable. A colostomy was effected using the upper part of the descending colon, and the median incision closed.

On July 1, 1936, the abdomen was reopened. The growth was mobilized by resecting the parietal peritoneum to which it was attached, and also some omental attachments, with the Percy cautery. The mesosigmoid was long and contained numbers of hard lymph nodes about the size of beans. About six inches of the sigmoid, including the tumor, was resected with the cautery and the ends of the sigmoid were joined end-to-end. The colostomy stoma remained open above the site of resection. The small bowel was packed off with gauze, it and the abdominal wall were protected with lead. The spinal anesthesia having begun to wear off, a second ampoule of pantocain was injected. 2,500 r, filtered through 3 Mm brass, 1 Mm of aluminum and 1¼ Mm tin, were administered through the open wound, after which the abdomen was closed. The patient made an uncomplicated recovery without nausea. A mild diarrhea occurred on the third and fourth days after operation, thereafter the stools were formed.

Pathologic Examination—Dr David A Wood reported as follows: There is a very firm, hard crater ulcer 3 cm in length, encircling the bowel wall, in the attached mesentery are a number of pale, very hard lymph nodes. The tumor is composed of fairly well differentiated but atypical glands lined by columnar epithelial tumor cells. The tumor has infiltrated the circular layer of muscularis. No tumor was found in the lymph nodes. *Diagnosis* Adenocarcinoma of colon.

On August 28, 1936, the colostomy stoma was closed. No tumor was to be felt in the anterior abdominal wall at the site of the previous resection of the peritoneum, no mesenteric nodes were seen or felt. The liver was not examined. No tumor was found on microscopic examination of the tissues of the resected colostomy opening.

The man has had no evidence of recurrence. The chance that he would remain free from recurrence seemed somewhat better than that of the first patient, still, the peritoneal attachment made the outlook doubtful.

Case 3—Adenocarcinoma of the Retrosigmoid Junction (Grade 3) with Lymphatic Metastases, Invading the Mesentery. J P, male, age 61. Referred by Doctor Gomez of Oakland. For four months he had been passing blood and mucus from the rectum. On rectal examination in the squatting position one could just touch a hard mass when the patient strained. Celiotomy, January 13, 1937, disclosed a scarred mass, invading the mesentery, some seven or eight inches above the anus and attached to the left side of the pelvis. Along the vessels were small hard nodes and an infiltration of the mesenteric fat. No nodes could be felt higher up and no liver metastases were palpable. There was no ascites. The bowel was severed six or seven inches above the tumor and the sigmoid extirpated with the Percy cautery from above downwards to about four inches above the

anus As much as possible of the fat in the left side of the pelvis was also removed The anal stump was closed and covered with peritoneum The wound was shielded with lead, so that the empty pelvis lay exposed and 3 100 i were administered through 2½ Mm of aluminum with a ray pointed at the left side of the pelvis The upper stump of the colon was implanted into a separate incision and the abdomen closed No nausea or diarrhea followed the operation

Pathologic Examination—The lymph nodes and lymphatic channels of the mesentery were filled with a typical adenocarcinoma, Grade 3 The bowel contained a carcinomatous plaque with a crater, there were a few nodules on the outer side of the bowel Convalescence was disturbed by anorexia

On March 6, 1937, the abdomen was reopened There was no demonstrable recurrence, the colostomy opening was freed and implanted into the anal stump On May 1, 1937, a periproctal infiltration was felt around the site of union, which may have been inflammatory There was no recurrence to be seen through the proctoscope and no bleeding had occurred into the bowel

The time of observation, four and one-half months, is too short to judge of results The prognosis for this cancer, Grade 3, with metastases in the nodes and in the mesenteric lymphatics, under the ordinary methods of treatment is extremely bad

Case 4—Double Adenocarcinoma of Jejunum and Right Ovary Pelvic Recurrence 15 Months Later Reoperation with Cautery, Extirpation and Irradiation Probably Recurrence for the Second Time McK, female, age 45, was first seen September 26, 1935, complaining of menstrual irregularity and abdominal colic of two months' duration At operation, October 12, 1935, a cystic tumor of the right ovary, the size of a grapefruit, was removed and also a scirrhus stenosing tumor of the jejunum, with involvement of the mesenteric lymph nodes The left ovary had been removed at an operation years before There was no ascites and no metastases were found

Pathologic Examination of the resected jejunum and of the ovary led to the diagnosis of double carcinoma, an adenocarcinoma of the jejunum with metastases in the mesenteric lymph nodes and a second independent adenocarcinoma of the ovary

The patient made an uncomplicated recovery In November, 1936, she complained of much pain in the right lower abdominal quadrant with severe radiation down the right leg, which was relieved by irradiation of the pelvis The pain recurred and in November a hard mass was felt adherent to the right side of the uterus The pain becoming intolerable, the abdomen was reopened January 19, 1937 The omentum contained a hard carcinomatous nodule adherent to the abdominal wall There were numerous nodules, mostly subperitoneal but also intraperitoneal ones, lying in the omentum, and one large mass lying subperitoneally in the remains of the broad ligament There were nodules between the uterus and the bladder and several others which invaded a loop of the lower ileum One involved the uterus itself The uterus was removed by a subtotal hysterectomy and as many of the nodules as could be felt were removed with the galvanocautery, working partly subperitoneally and denuding the wall of the pelvis to a considerable extent The involved loop of ileum was then laid on the abdominal wall, which was shielded with lead plates and the pelvis was filled with gauze It was not possible to shield the right half of the bladder About 2,250 r, filtered through ¼ Mm of copper and 1 Mm of aluminum, were administered through the open wound The involved loop of ileum was resected for a distance of about six inches and the wound was closed It was possible to cover the left side of the pelvis with peritoneum only under tension and by utilizing the rectum itself as a covering

Pathologic examination of the removed tissues showed the presence of metastatic carcinoma, composed of irregular atypical glands lined with short columnar and polyhedral epithelial tumor cells

The patient recovered from the operation She had no diarrhea or nausea, nor symptoms of damage to the bowel She was freed of pain in the hip and leg However,

in April, 1937, hard nodules about the size of walnuts, fixed to the right pelvic wall, and an induration to the left of the rectum made themselves apparent

Case 5—Rapidly Growing Carcinoma of Cardia with Esophageal Extension and Metastases to Mediastinal and Abdominal Lymph Nodes Irradiation and Gastrostomy C P, male, age 55, was first seen May 19, 1936. He had had attacks of upper abdominal pain for 16 years. In March, 1936, he began to have difficulty in swallowing. Esophagoscopy and biopsy revealed a rapidly growing small cell adenocarcinoma of the cardia. At operation, May 22, 1936, a large nodular carcinoma with lymphatic metastases was found at the cardia. There was an infiltration extending into the lower esophagus and numerous carcinomatous lymph nodes in the lower mediastinum. The liver and the bowel were protected with lead and an attempt made to shield off the pancreas by placing two narrow strips of lead across the stomach over the pancreas. 3,000 r, filtered through $2\frac{1}{2}$ Mm of aluminum were administered through the open abdomen, a Witzel gastrostomy was effected and the abdomen closed. The patient made an uninterrupted recovery, and was discharged June 6, 1936. Swallowing was somewhat improved for a time, then grew worse and death ensued, August 2, 1936, from inanition and a terminal pneumonia following large doses of barbiturates.

Case 6—C K, female, age 33, whose brother had died of cancer of the stomach, began to complain early in 1936 of fatigue and gastric disturbances. At operation, August 19, 1936, the whole greater curvature of the stomach from the pylorus to the cardia was found involved by a hard lumpy mass. There were enlarged lymph nodes at the celiac axis. Using the Percy cautery, a total gastrectomy was performed and the lymph nodes were removed as well as possible. The cardia was united to the jejunum and 3,000 r were administered to the open abdomen, through $2\frac{1}{2}$ Mm of aluminum.

Pathologic Examination—Dr David A. Wood reported that the resected specimen showed infiltration of the submucosa and muscularis with small polyhedral epithelial tumor cells. *Diagnosis*—Carcinoma of the stomach (limitis plastica).

Recovery was delayed by the formation of a fistula from the blind duodenal stump, which discharged duodenal secretion, but healed spontaneously in a few weeks. Much more disturbing was a constant and inexplicable nausea, which still continues nine months after operation. This nausea and feeling of seasickness come on immediately after eating, or even at the sight of food, but are never accompanied by vomiting. Attempts to explain them have failed, there have been no diarrhea, no evidence of pancreatic achylia and no signs of bowel obstruction. Under the fluoroscope one sees some regurgitation of barium into the duodenal loop, the barium, however, soon leaves this loop and runs rapidly down into the small bowel. The duodenal loop is not distended. All efforts at overcoming the nausea have failed. There has been no evidence of recurrence.

SUMMARY

A method of administering roentgen radiation to the open abdomen for cancer of unusually grave prognosis is described. By this method uninvolved, vulnerable organs and tissues are shielded from irradiation. The source of energy is approximated to the cancer and heavy filtration is dispensed with.

REFERENCE

- ¹ Duggar. *Biological Effects of Radiation*. McGraw-Hill Book Co., New York and London, 1936. Gives the theoretic foundation for this method and contains an extensive bibliography.

CARCINOMA OF THE CERVIX TREATED BY THE ROENTGEN RAY AND RADIUM

JOE VINCENT MEIGS, M D , AND RICHARD DRESSER, M D

BOSTON, MASS

FROM THE PONDVILLE HOSPITAL, MASSACHUSETTS STATE CANCER HOSPITAL, AND THE MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MASS

THIS paper is a presentation of a method of radiation treatment in use at the Pondville Hospital, and of the results obtained three and one-half years after its employment. A few comparisons are made to another method of therapy, familiar to the authors, and to the results obtained. No method of treatment of this disease will increase the "cures" to a much higher percentage except earlier diagnosis of the condition. Such early diagnoses are possible through routine examinations of the cervical epithelium with Schiller's iodine solution test and the colposcope. Only by constant use do these methods help in making the diagnosis, but once learned, and used frequently, early cases should be found. In most series the number of so called operable cases is given as from 15 to 25 per cent, and in most operated or surgically treated series the number of lymph node extensions is given as 33+ per cent. Thus in any series the early cases are few and metastases common. Twenty to 30 per cent of five year cures indicates excellent results from treatment. By the method herewith presented the results, in a series of 70 cases, show 35.7 per cent living and well and without disease three and one-half years after treatment. All cases reported as having disease after three and one-half years have been classified as dead. Since there was only 11 per cent of early cases in the group, such results are better than usual and hence offer the excuse for this early report.

The Pondville Hospital opened in 1927. At that time the recognized method of treating carcinoma of the cervix in Boston was that advocated by G. A. Leland, Jr.,¹ at the Collis P. Huntington Memorial Hospital. His method of treatment had been introduced into the Tumor Clinic of the Massachusetts General Hospital on its opening, in 1925, and thence into the newly opened Pondville Hospital. The radium used at the Massachusetts General Hospital is from a general pool at the Huntington Memorial Hospital—in an emanation plant—and is available but one day each week. Because of Leland's success and because his form of treatment does not last over 24 hours and necessitates the use of hospital beds for a period of only four days, it was adopted at the Massachusetts General Hospital and is still in use at the present time. During the first four years at the Pondville Hospital the types of cases (mostly secondary and far advanced) were not suitable for starting a new form of treatment with any hope of success, so the treatment used at the Huntington Memorial Hospital and the Massachusetts General Hospital was begun, and careful observation of the

effects of the treatment maintained. After four years of observation it was decided by the roentgenologist (Dr Richard Dresser) and the surgeon (Dr Joe V Meigs) that an entirely different method should be introduced. In 1931, after carefully weighing all the facts and realizing that our theoretic approach might not be so good as the tried method, a new series was begun. It was decided that we should carry out the method outlined herewith, until a satisfactory number of cases had been followed for a sufficient number of years to determine whether or not the new treatment was worth while. We are both convinced of the success of this method and intend waiting before any additional change is made until a five year follow up is available in a given group of cases, but we have decided to report our group as it stands at the present time—a three to five year posttreatment study.

The Two Methods of Treatment—As a comparison of end-results is to be made between the two methods of treatment, a brief description should be presented of Leland's plan, though his own report¹ must be read for a more detailed explanation. Next the Pondville method will be presented with the reasons for its employment.

In the main, the plan of treatment in use at the Huntington Memorial Hospital consists of the use of a large amount of radium emanation over a short period of time. Gold seeds of approximately 1 mc each are placed at a depth of 1 cm about 1 cm distance from each other around the periphery of the growth and a silver cylinder 1 Mm in thickness containing a steel needle with a glass emanation tube inside is placed in the cervical canal. The total dose is given from 3,500 mc hours, in the moderately advanced cases, to 5,000 to 6,000 mc hours in the early cases. The seeds make up from 1,300 to 1,500 mc hours of the dose and the radium in the silver cylinder the remainder. This form of radiation is a combination of the *beta* and *gamma* type, and sloughing and destruction of tissue are often seen. The advanced cases are treated by means of a cylindrical 2 Mm lead applicator containing radium emanation with or without gold seeds.

The Pondville plan of treatment, which, in the authors' minds, was a rather new type of attack, is now an old story to many workers in the field of radiation (Coutard,¹¹ Healy,² Schmitz,³ and others). We felt that in the seed and central applicator method of treatment, emphasis was placed upon the destruction of tissue by the cauterizing effects of the radiation rather than upon the specific action of *gamma* rays upon growing tissues and dividing cells. The roentgen ray was not utilized at all, and tumors of all sizes, conditions and appearances were treated. It seemed to us that the roentgen ray could be utilized for two purposes: first, to help shrink down a large cervical growth and to clear up an infected one, and second, to cause an increase of connective tissue and a lessening of blood supply in the region adjacent to the cervix. We hoped to make the field next to the cervix less permeable to the growing cancer but did not feel that the roentgen treatment alone would kill tumor cells already there. Next we felt

CARCINOMA OF THE CERVIX

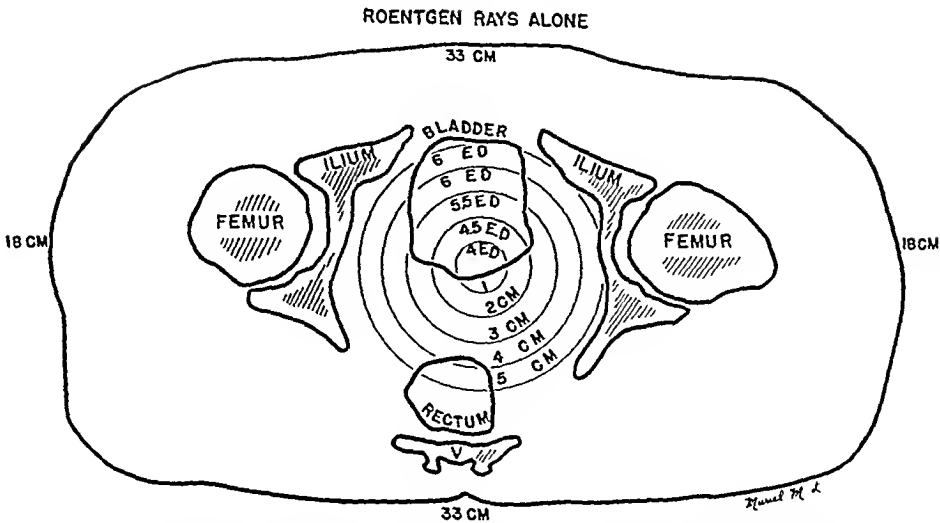


FIG 1—Anatomic chart showing the Pondville roentgen radiation plotted in erythema doses at centimeter intervals from a central point presumed to be the center of the cervix

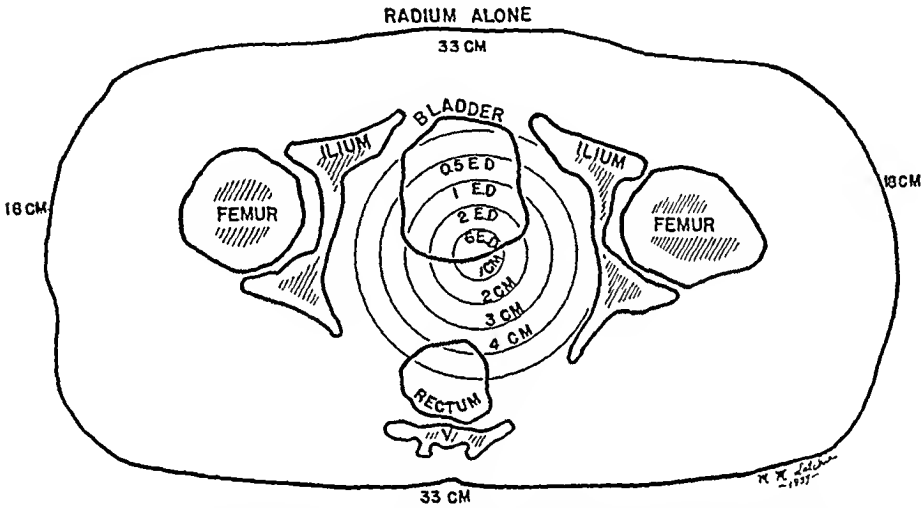


FIG 2—Radium given in two divided doses of 1500 millicurie hours each. The number of erythema doses are plotted at centimeter intervals from the center of the cervix. Notice how rapidly radium strength falls off from a point source

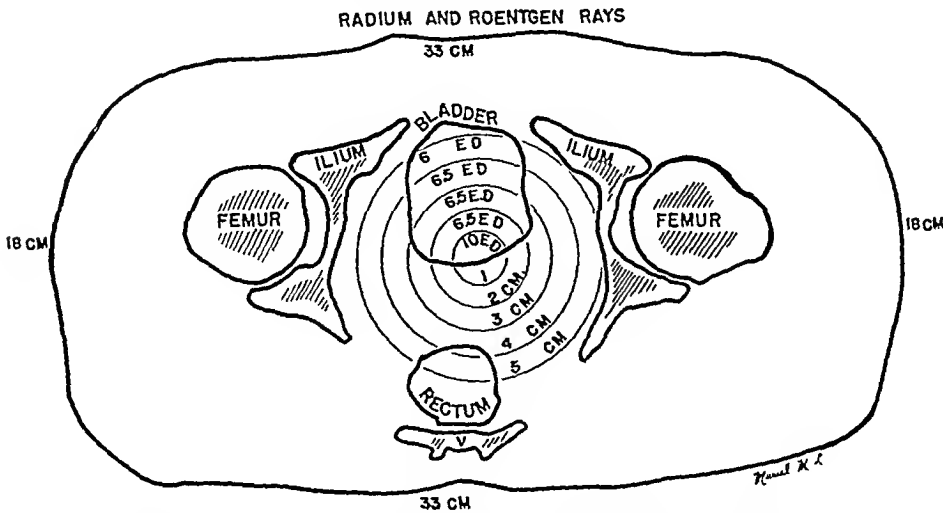


FIG 3—Showing the number of erythema doses delivered at centimeter intervals by a combination of roentgen and radium treatment as described in the text

that it would be best, in our first series, to limit the use of radium to one set type of application so that all treatments would be as uniform as possible. We considered that a total dose of 3,000 mc plus the radiation by roentgen ray might be all the patients could tolerate. It appeared to us that a division of the 3,000 mc dose of radium might be less likely to cause sudden and extensive destruction of tissue and therefore less possibility of injury to the bladder or rectum. Another reason for dividing the dose of radium was the confirmation of the work of Canti^{4 5} and his coworkers, who demonstrated that on the fourth day after radiation with radium, there is a sudden sharp rise of abnormal mitotic figures. Their work was repeated upon radium treated cases at the Huntington Memorial Hospital, by Frederic Parker, Jr., and Meigs,⁶ and this phenomenon proved. It seemed reasonable, therefore, to choose the fourth day as the best day for the second dose of the divided radium treatment. It is possible that the previous roentgen radiation might spoil this phenomenon but this has not been confirmed as yet. Thus the plan was to increase the resistance of the pericervical and parametrial tissue to the invasion of cancer and to destroy or prevent tumor cells from dividing, incidentally, such treatment might reduce the size of the cervical growth and perhaps produce a cleaner and less infected field to work in. One other consideration entered into our plan and that was that the radium treatment had to be given in almost every instance by a member of the Resident Staff and that therefore it must be made as fool proof as possible. Inasmuch as the surgeons in charge of treating cervical cancer at Pondville visit the hospital but once a week, and as the radium had to be given four days apart, it was not possible for the treatments to be given by the Visiting Staff.

The roentgen ray treatment at Pondville is given as follows, and is completed in an average of 14 days. Four portals of entry, 8x10 and 10x10 cm., are employed, two anterior and two posterior. The rays are directed obliquely at the cervix and parametrium by means of a special centering device. Each field receives a total of 1,500 to 2,000 r units (air measurement), the total dosage depending on the rapidity with which the treatment is given. Daily exposures of from 300 to 600 r have been used alternating the fields so that a given area receives an exposure every fourth day. The machine setting is as follows: 200 kv peak, 5 to 20 ma, depending on the capacity of the apparatus, 1/2 Mm copper filter, 50 cm focal-skin distance. It has been found by ionization measurements made in a press-wood phantom and also by measurements made in the human pelvis that distances greater than 50 cm do not appreciably increase the depth dose. It is assumed that 1,200 r measured with back scattering with the ionization chamber in the half submerged position produces a mild erythema. By means of roentgen radiation alone a total of four to six erythemas are delivered to an area 10 cm in diameter or to the region of the cervix in the patient of average size (Fig 1). Figure 2 illustrates the distribution of radiation in terms of skin erythema doses when using an intra-uterine

radium application of 3,000 mc hours. It will be noted that at a distance of 1 cm from the applicator six erythemas are delivered by radium, at a distance of 2 cm two erythemas, and at 3 cm only one erythema. The augmented dose of six to ten erythemas delivered by roentgen radiation combined with an intra-uterine radium application of 3,000 mc hours is shown in Fig. 3.

Radium emanation is used in the treatment and it is collected in a capillary glass tube which is held in a steel jacketed needle of 0.1 Mm thickness. The needle or needles are then placed in a platinum applicator of 1 Mm thickness, which is inserted into the cervical canal after sufficient dilatation. All patients are operated upon under a light general anesthesia. The applicator is then retained in place by suturing the ring of the applicator to the cervix by means of the method described by the late John G. Clark.⁷ The vagina is filled loosely with one or more strips of gauze. On occasion, when it appears to the operator that the pack might become loosened or dislodged and the applicator slip, the vulva is sutured across over the pack with silk sutures (it is recognized that there is danger of implantation connected with this procedure but no complications or harmful effects have as yet been encountered). A constant drainage catheter is then placed in the bladder to keep it empty and the radium is left in until a dose of 1,500 mc hours has been given. On the morning of the fourth day the patient is again taken to the operating room and under an anesthetic the applicator is reapplied. The time of the radium treatment depends upon the strength of the radium in the applicator: the more radium emanation present the shorter the time, and vice versa. No attempt is made to give the treatment either over a short or over a long period of time. The total dose given is 3,000 mc hours in two divided treatments four days apart.

Discussion of the Treatment—The form of treatment described above in use at Pondville, since June, 1931, is unique only because of the use of a set amount of radium of small dosage given in two equally divided treatments in the cervical canal only, and given four days apart, directly after radiation by roentgen ray is finished. The roentgen ray, given as it is, to cross fire the cervix and to radiate the pericervical and parametrial tissue, is satisfactory, and Dresser has presented his reasons for not using a longer focal distance. It is possible that the new 400,000 to 1,000,000 volt machines with their ability to deliver a greater number of "r" units to the broad ligaments in a shorter period of time with less skin injury will produce great changes in the method of roentgen treatment. With the present 200,000 volt machines it is felt that the limit of roentgen treatment has been reached.

The weakness of our treatment lies in the radium plan, and without doubt the destruction of the growth of the cervix itself might be accomplished more satisfactorily with a more diffuse treatment. The problem is to get more radium into the vaginal extensions of the tumor and into

the tissues in the pericervical regions just about the cervix without injury or destruction of normal tissues. The actual region of the growth is the weakest spot and our revised attack will probably take some form of colpostat, low strength interstitial radiation, vaginal plaques, or a combination of them all. The very fact that tumors of the cervix grow in many different shapes and sizes, and are outgrowing and ingrowing, means that any fixed type of treatment cannot be satisfactory if it necessitates the use of any inflexible surgical instrument. The satisfactory treatment of a cervical cancer depends upon the ability of the operator to use any sort of radium container or applicator that will enable him to obtain a *diffuse* radiation of the affected parts. It is of no use to present a method of treatment unless such treatment is so flexible that it can take care of any cervical cancer. The recent method at Pondville is flexible, but in widespread growths with large tumor masses in one quadrant of the cervix the radium dose given in the cervical canal is not heavy enough to obtain proper radiation in the distant areas. We have recognized this difficulty and will correct it, but it was first necessary to establish what this method would accomplish. Having had experience with the two types of treatment outlined above, there is no doubt that the newer method is better and that our future therapy will be a modification of it.

Pathology—At the outset it was the determination of the authors that the effect of the radiation on the tumor should be followed through the various stages of treatment, so a biopsy is therefore taken before the roentgentherapy is started, after it is finished, and after the first radium application, but unfortunately not after the second radium dose until the last year. The most striking observation from our study of the material is the lack of uniformity of the successive biopsies as regards the grading into low, medium, and rapid growth. There seems to be no consistency in the grading and often all three grades of carcinoma are found in the same tumor at different stages of treatment, even specimens taken on the same day. Often before the first radium application there will not be sufficient carcinoma for grading, or perhaps radiation necrosis only will be present.

The question of whether or not changes in the grade of malignancy after radiation had any bearing on the prognosis was answered in the negative. A change in grade from 2 to 1 was followed by the best results but the number of cases was too small to be of any real significance. Those patients in whom the grade did not vary were next best while those with changes from a 2 to a 3 or a 3 to a 2 did poorly. It is our opinion that the grade changes frequently and no reliance can be placed upon it. Perhaps when many more patients have been treated and followed changes in grades may have more significance.

It is evident from our study that those patients with an original biopsy of a medium or Grade 2 malignancy do better than the others, both in the Pondville and Massachusetts General Hospital series (Table I). After

CARCINOMA OF THE CERVIX

TABLE I

GRADE OF MALIGNANCY

Pondville—70 cases

Grade 1	20% of 5 cases living 3½ years
Grade 2	41 3% of 29 cases living 3½ years
Grade 3	29 1% of 24 cases living 3½ years
Adeno	66 6% of 3 cases living 3½ years
?	33 3% of 9 cases living 3½ years

M G H—Radium—150 cases

Grade 1	18 2% of 11 cases living 3½ years
Grade 2	29 4% of 34 cases living 3½ years
Grade 3	21 2% of 80 cases living 3½ years
Adeno	28 5% of 7 cases living 3½ years
?	25 2% of 18 cases living 3½ years

M G H—Surgical—60 cases

Grade 1	28 7% of 17 cases living 3½ years
Grade 2	48 1% of 27 cases living 3½ years
Grade 3	20% of 10 cases living 3½ years
Adeno	0% of 3 cases living 3½ years
?	100% of 3 cases living 3½ years

*Analysis of the grades of malignancy in the groups showing that Grade 2 is most commonly followed by a successful result

the roentgen treatment those tumors showing microscopically "radium reaction only" gave the best results. After the first radium application a report of Grade 3 was most favorable, but if the cancer could not be graded and "radium reaction only" was present, the outlook was almost as favorable. The study faintly foretells a favorable result if a change in grade is found or if the examination shows "radium reaction only" but there are no consistent findings. A much larger series of cases is needed and further study is necessary before any deductions can be made.

Apparently the results do show that the malignant part of the cancer is most affected by our treatment and that if the cancer is very sensitive to radiation most of it will disappear early, leaving only necrosis behind. But this does not necessarily signify a favorable result.

Undoubtedly the biopsies depend upon the individual operator and the area from which the specimen is taken, but it is our opinion in reviewing the cases that there is no persistent grade of malignancy once the treatment has been started. It is evident that the roentgen treatment affects the tumor in the cervix nearly always. Grading has come to mean less and less to us as a guide to prognosis because of the variations present in each individual tumor as seen in the successive biopsies.

Effect of Treatment—This method seems to one who has followed many cases of cervical carcinoma undergoing treatment by far the most gentle and easiest, for the small divided doses of radium cause very few disturbances. It was considered evidence of a severe reaction to the roentgen treatment if the patient complained of nausea, vomiting, anorexia, diarrhea, or if it was necessary to stop the treatment. There were 25 such cases but

none in whom the plan could not be completed. All patients who are not in fair general condition are put on a nourishing diet and transfused if necessary before the treatment is started, and they seem to improve rather than fail as therapy progresses. Frequently during the treatment the patient's discharge and bleeding ceases and a general feeling of well-being commences.

Often the gross appearance of the cervix changes after roentgen treatment, and the tumor is found to be smaller, firmer, and less infected, and sometimes the whole lesion has healed over and the cervix looks fairly

TABLE II

SHRINKAGE OF TUMOR FOLLOWING ROENTGEN
TREATMENT IN 19 CASES*

Grade 1	0
Grade 2	10 or 34 5% of total
Grade 3	7 or 29 1% of total
Adeno	1 or 33 3% of total
?	1 or 11 1% of total

* This demonstrates that the Grade 2 tumors most frequently showed a definite shrinkage of the tumor closely followed by Grade 3 tumors.

normal. This, however, is deceiving, for on dilating and curetting the cervix obvious cancer is found and larger pieces of tissue can be easily scraped away.

Nineteen patients, or 27 per cent, showed a real shrinkage of the tumor (Table II) following roentgen treatment and although this is but a small percentage of the total group, it is nevertheless an important observation. It is interesting that the Grade 2 cancers, or those of medium malignancy, showed a greater percentage of shrinkage of tumor than did the Grade 3, or rapidly growing tumors, the difference in percentage is not very striking. Many more tumors probably shrank, though the observation was not recorded, and it is expected that in the next group this finding will be more common.

At the first radium treatment it is sometimes impossible to locate the cervical canal, in which case it is necessary to use the so called lead bomb, or 2 Mm lead cylinder, but after this, at the second radium application, it is usually easy to locate the canal. It is not often that the canal is not found on the first attempt, but it must be remembered that the treatment is usually given by an intern who may lack experience in this sometimes difficult feat. The usual swelling and pussy discharge, so common in cancer of the cervix, is often present during the first part of the therapy, but it is uncommon for a severe reaction to follow any of the treatments. There are the usual number of pyometria due to stenosed cervixes, but treatment even in these cases proceeds without undue difficulty.

Dr Roger C Graves,^{8, 9} urologist at Pondville, and his coworkers who have charge of investigating the urologic complications of this disease,

CARCINOMA OF THE CERVIX

have found no bladder changes such as are seen in the more destructive forms of treatment, and our attention has been called again and again to this fact. The usual number of fistulae develop, if the cancer has penetrated the bladder, but there are no fistulae which the operator can attribute to the radium itself. Renal involvement due to cancer involving the region of the ureters is just as frequent as in any other method, for there is no treatment devised that will kill cancer cells once they have surrounded the ureter. The growth may be checked but the damage done to the ureter is usually persistent and cannot be relieved by any method of radiation therapy.

TABLE III

ANALYSIS OF THE PONDVILLE CASES

Married	69
Single	1
Children	60
No children	9 or 12 8%
Positive Wassermann	5 or 7 1%
Genito-urinary involvement	19 (18 or 94 7% dead)
Pain as symptom	15 or 21 4%
A	1
B	1
C	7
D	6
Fever in hospital	12 or 17 1% (all dead)
C	10
D	2

Nineteen patients (Table III) had involvement of the urinary tract as shown by cystoscopy, pyelogram, or autopsy, and all but one have succumbed to the disease. Thus the extension of disease as shown by urologic investigation places the patient in a different group and the prognosis is grave. Of the patients in the hospital who, during treatment, ran a temperature of 100° F or over for a period of a week or more, none are living. Some of these were among those with renal involvement or ureteral block.

The convalescence is not difficult and few patients have long bouts of severe pain or difficulty when they return home. There is not the same need for the use of morphine and sedatives as in the older form of treatment. The patients do not complain of rectal tenesmus and bladder irritation as they often do when a destructive *beta* radiation has been given.

In many instances there remains on the abdomen, indefinitely, evidence of the roentgen treatment and if it is not present, it is obvious that the dosage might be repeated or increased. Areas of epilation are frequently present and usually persist. Occasionally the very brown skin and thick subcutaneous tissue of the typical severe radiation reaction is found. These areas are often tender for many months but gradually clear up, leaving a deep, dark, scarred area covered with telangiectases.

Results—The group of cases presented are those who, in 1931, 1932,

and 1933, were given a typical treatment as described above. No selection of cases was made and they were treated as they arrived at Pondville. The only qualification was that they be primary cancers of the cervix that had had no previous roentgen therapy or radium treatment or a supra-vaginal hysterectomy. In other words, this is the report of the results of a group of 1A, 1B, 1C, and 1D cases as grouped by the American College of Surgeons classification. There were five 1A, three 1B, 45 1C, and 17 1D cases. The distribution is about as typical as in other series reported and it can be seen that there has been no selection of cases.

The authors realize very decidedly that a three and one-half year follow up, of itself, is of very little significance, but the results will be compared to (1) A group of cases that have had no treatment at all (as compiled by Welch and Nathanson¹⁰ of Boston and soon to be published in detail), (2) to a group operated upon by Dr. Lincoln Davis and Dr. Farnar Cobb at the Massachusetts General Hospital, and (3) to a series radiated by the Huntington Memorial Hospital method at the Massachusetts General Hospital by Drs. Lincoln Davis, Langdon Parsons, Charles Swan, and Meigs. These are of necessity reported on a basis of the percentage of patients alive at one year, one and one-half years, two years, etc., as all series are

TABLE IV

DISTRIBUTION OF CASES IN EACH GROUP, AND RELATIVE PERCENTAGE
LIVING AFTER ONE, TWO, THREE AND THREE AND ONE-HALF YEARS

	A	B	C	D	?	Total
<i>Totals</i>						
Pondville	5	3	45	17	—	70
M G H—radium	15	13	100	22	—	150
M G H—surgical	28	11	20	1	1	60
<i>Living One Year After Treatment</i>						
Pondville	5—100%	3—100%	28—62 2%	10—58 8%	—	46
M G H—radium	14—93 3%	8—61 5%	56—56%	8—36 3%	—	86
M G H—surgical	20—71 4%	7—63 6%	10—50%	—	—	37
<i>Living Two Years After Treatment</i>						
Pondville	5—100%	3—100%	23—51 1%	2—11 7%	—	33
M G H—radium	14—93 3%	7—53 8%	37—37%	3—13 6%	—	61
M G H—surgical	18—64 2%	7—63 6%	6—30%	—	—	31
<i>Living Three Years After Treatment</i>						
Pondville	5—100%	3—100%	21—46 6%	1—5 8%	—	30
M G H—radium	13—86 6%	7—53 8%	28—28%	3—13 6%	—	51
M G H—surgical	17—60 7%	6—54 5%	5—25%	—	—	28
<i>Living Three and One-Half Years After Treatment</i>						
Pondville	5—100%	3—100%	16—35 5%	1—5 8%	—	25
M G H—radium	12—80%	7—53 8%	18—18%	—	—	38
M G H—surgical	13—46 4%	5—45 5%	5—25%	—	—	23

CARCINOMA OF THE CERVIX

of different sizes and a comparison by numbers living and well would therefore not be satisfactory (Table IV)

The radiated cases at Pondville and the Massachusetts General Hospitals have been combined and have been plotted against the curve of untreated cases (Chart 1) The comparison is from the onset of disease to a five year period, or as long as the treated cases have been followed It

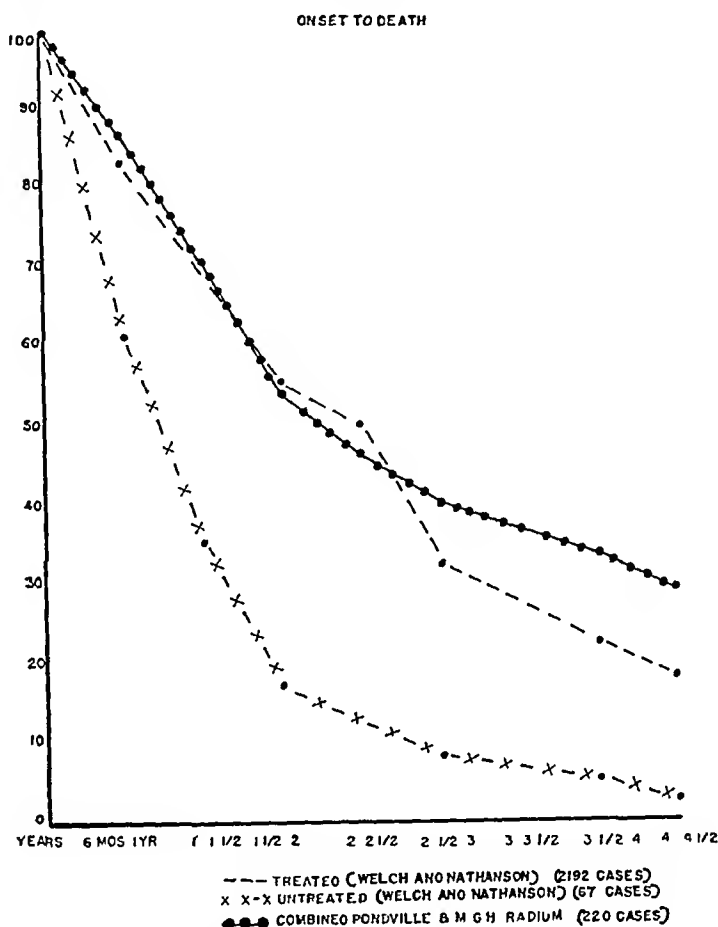


CHART 1—Showing the combined Massachusetts General Hospital and Pondville cases plotted against a large group of treated cases of all types (2,192 from the Huntington and Pondville Hospitals, compiled by Welch and Nathanson), and against Welch and Nathanson's curve of 67 untreated cases. These are calculated from the onset of disease. Primary cases (Pondville and Massachusetts General Hospital) carefully treated obviously do better than the untreated or the unselected.

can easily be seen that as a group, radiated cases compare very favorably to untreated cases

The comparison between the two series of radiated cases (Chart 2) from the time of treatment until a three and one-half year period has elapsed shows a very distinct advantage in favor of the Pondville cases—35.7 per cent compared to 24.6 per cent. It must be remembered that in these groups all patients with disease at three and one-half years are classified as dead, and in comparing groups of only 70 and 150 cases each mistake changes the percentage greatly. However, it is evident that most deaths occur within two years and that a three and one-half year follow up

on this basis is fairly accurate if comparatively few patients die who are without disease after two years. We believe that this is a fair method of reporting our results and that a record of progress is indicated after three and one-half years, because at some time a comparison and an evaluation of a given method of treatment must be made. If one were to wait five

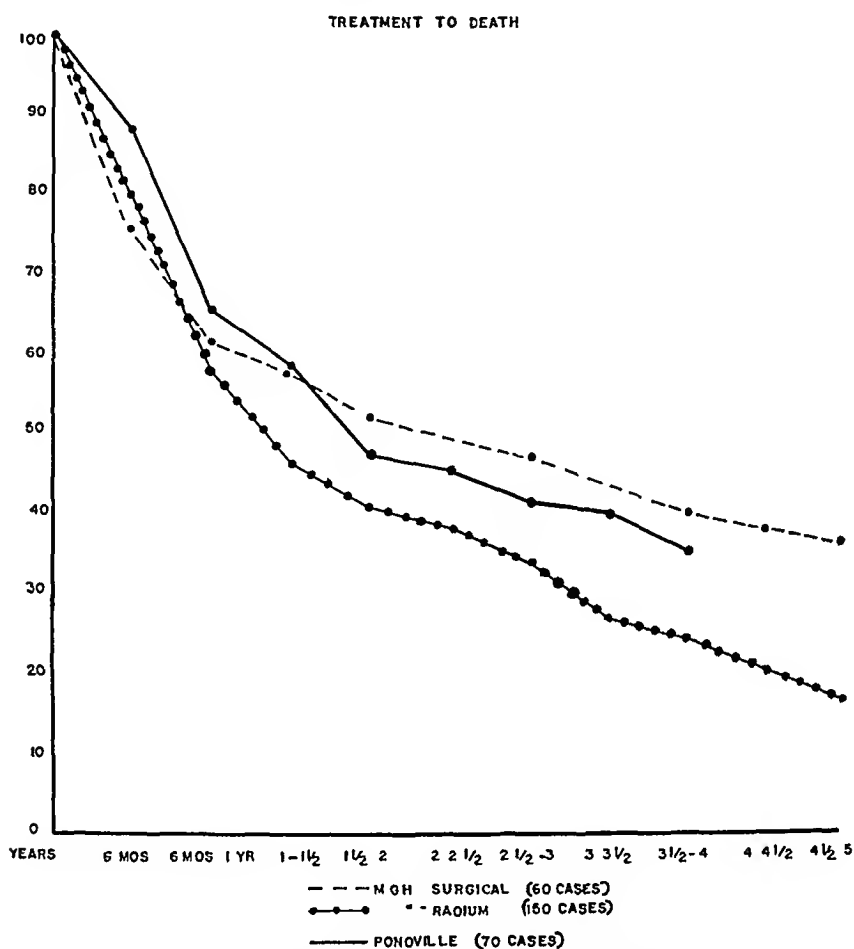


CHART 2—The surgical cases were operated upon by a modified Wertheim technique and include only favorable cases. The Pondville cases if the curve keeps on as it is will have a better five year curability percentage than the Massachusetts General Hospital radium cases.

years before each change in treatment, there would be time for only four or five changes in the lifetime of any one surgeon, and surely indicated changes should keep pace with the growth of the surgeon's experiences and knowledge of this disease.

Of 70 patients in the Pondville Hospital series, 35.7 per cent are living and without evidence of disease after three and one-half years. It is obvious that a few of the living and well after three and one-half years will succumb before five years, but the number has been reduced to a minimum by the careful exclusion of patients with disease after three and one-half years. Of the early or operable cases, Group 1A and 1B, all are alive and well and without evidence of disease. Our most striking results are in

CARCINOMA OF THE CERVIX

the 1C cases (Table V) for in this group 35 5 per cent of 45 patients are alive and without evidence of disease This is a marked improvement over the Massachusetts General Hospital series, which shows only 18 per cent of 100 cases living, and offers most encouragement for the newer method of treatment It must be remembered that in this Pondville group a diffuse radiation by radium was not given and thus many tumors that

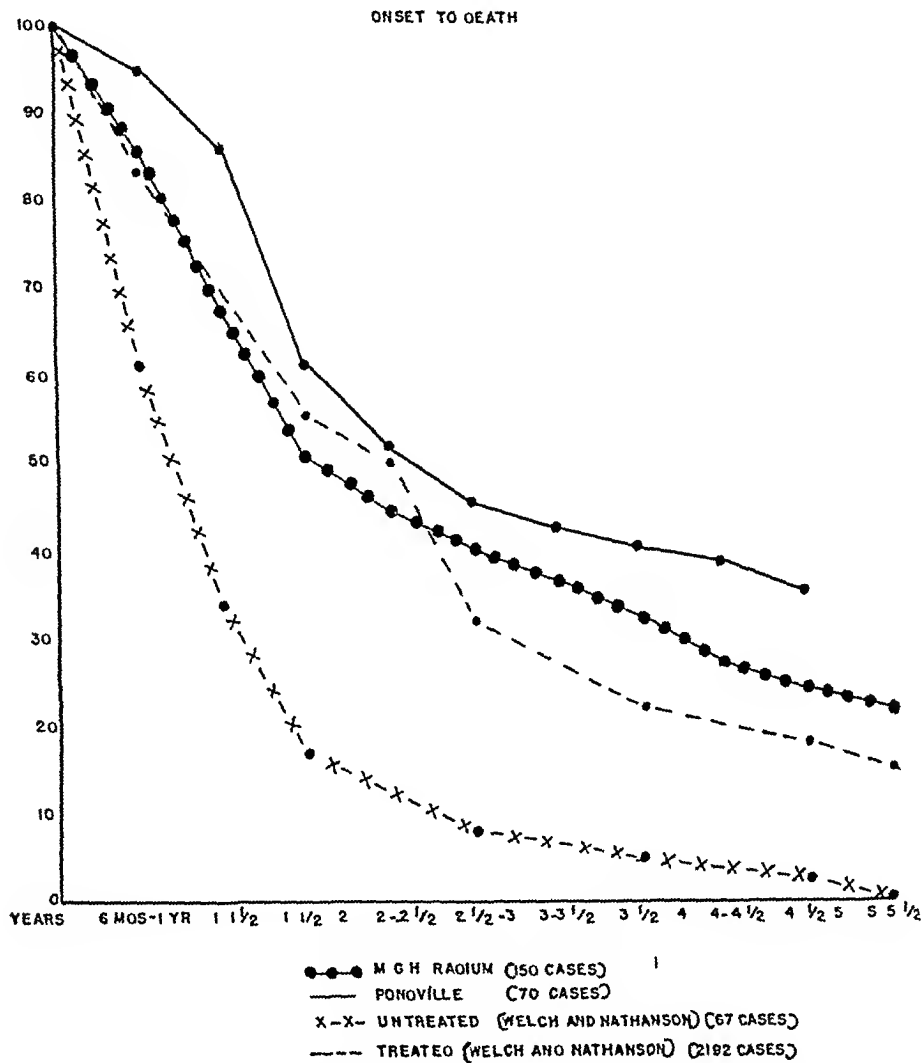


CHART 3 —Showing the results from onset of symptoms of the various series The end result of the Pondville cases will be better if the general trend of the curves keeps on

had extended into the vaginal walls and into the pericervical tissues are, extraordinarily enough, free from disease

TABLE V

ANALYSIS OF THE RESULTS OF TREATMENT IN THE PONDVILLE CASES

	A	B	C	D	Total
Number	5	3	45	17	70
Percentage living	100	100	35 5	5 8	35 7
Symptoms to treatment	10 4 mos	4 8 mos	8 2 mos	8 6 mos	
Treatment to death			18 mos	13 7 mos	
Symptoms to death			25 mos	22 4 mos	

In an analysis from all points of view, it has not been possible to find any common factors that would suggest a favorable or unfavorable outcome other than the extent of the disease. The duration of symptoms in our earliest cases (IA) was longer than in our next group (IB). The type of individual—fat or thin, old or young—does not seem to influence the result. Because certain patients that are similar in appearance and whose lesions are similar in size, shape, extent, and grade have a different outcome, the authors feel that the result in a given case of cancer of the cervix must depend upon the sensitivity to radiation or the resistance of the tumor, upon the unknown factors in the patient which are hostile to the disease, and upon the patient's ability to react favorably to treatment given to destroy the growth. A more careful and detailed study of favorable and unfavorable cases, in classes by themselves, may shed more light upon the prognosis as far as extent of disease, type of growth (outgrowing or ingrowing), grade of cancer, *etc*, are concerned.

CONCLUSIONS

(1) It is evident to the authors that the new form of radiation treatment developed at Pondville, simple in its execution and for that reason safely given by the Resident Staff, is an improvement over the Huntington Hospital method of treatment now in use at the Massachusetts General Hospital.

(2) There are many defects in the new form of treatment and perhaps with a greater use of roentgen radiation and certainly with a more careful attempt to obtain a more diffuse radiation with radium, better results will be obtained.

(3) When comparing the group of untreated cases with the group of treated cases, it is obvious that treatment of cervical cancer holds considerable hope for many women.

(4) It should be our aim to make the diagnosis of this disease earlier, before it has extended and involved the ureters, bladder, and rectum or metastasized into the lymph nodes, when there is no hope of any treatment effecting a cure.

REFERENCES

- ¹ Leland, George A., Jr. Radium in Treatment of Cancer of the Female Pelvis. *Physical Therapy*, 48, 281, 1930.
- ² Healy, William P. Experience with Multiple Dose Roentgen Therapy in Malignant Diseases of the Uterus and Ovaries. *Am J Obst & Gynec*, 30, 613, 1934.
- ³ Schmitz, H. Radiation Therapy in Carcinomas of the Uterine Cervix. *Radiology*, 23, 548, 1934.
- ⁴ Donaldson, Malcolm, and Canti, R. G. Fifty Cases of Carcinoma of the Cervix Treated with Radium. *Brit Med J*, 2, 12, 1923.
- ⁵ Canti, R. G. Effect of Irradiation on Tissues. *St Bartholomew's Hospital Report*, 60, 57, 1927.
- ⁶ Meigs, Joe V., and Parker, Frederic, Jr. The Effect of Radium on Cancer of the Cervix. *New Eng Jour Med*, 203, 247, 1930.

- ⁷ Clark, John G, and Norris, Charles C Radium in Gynecology J B Lippincott Company, 1927
- ⁸ Graves, Roger C, Kickham, C J E, and Nathanson, Ira T The Ureteral and Renal Complications of Carcinoma of the Cervix Jour Urology, 36, 618, 1936
- ⁹ Graves, Roger C, Kickham, C J E, and Nathanson, Ira T The Bladder Complications of Carcinoma of the Cervix Surg, Gynec & Obstet, 63, 785, 1936
- ¹⁰ Welch, Claude E, and Nathanson, Ira T Life Expectancy and Incidence of Malignant Disease, IV To be published
- ¹¹ Coutard, Henri Roentgen Therapy of the Pelvis in the Treatment of Carcinoma of the Cervix Am J Roentgenology, 36, 603, 1936

CANCER SURGERY

THE VALUE OF RADICAL OPERATIONS FOR CANCER AFTER THE LYMPHATIC
DRAINAGE AREA HAS BECOME INVOLVED

CARL EGGERS, M D

NEW YORK

OUR knowledge concerning cancer, its tendency to spread locally as well as along lymphatic paths and the blood stream, has been acquired gradually. With increasing knowledge methods of combating it have been developed. For the last half century the fundamental principle of cancer treatment has been the complete radical removal of the primary growth together with its regional metastases. As anatomic knowledge increased and the rôle of the lymphatic circulation in the spread of cancer was revealed, special operative procedures were devised to cope with cancers arising in each anatomic site. By patient study and work many of these operations reached a high degree of perfection and yielded gratifying results. Then came the introduction of irradiation therapy. Early reports were unusually favorable. Many experienced surgeons were willing to discontinue operating and to rely upon the new agent. When, after awhile, it was recognized that its use has certain definite limitations, the enthusiasm which followed its introduction began to wane. Today irradiation is recognized to be a valuable adjunct to surgery, but not the great panacea for cancer which it was originally proclaimed to be.

Irradiation therapy has not replaced surgery except in a few specific fields. In order to permit progress, it is essential to recognize the limitation of each therapeutic agent, and to base our teaching on facts.

It is important that the pessimistic attitude toward the entire subject of cancer, which is the prevailing one among the public as well as among the majority of medical men at the present time, be superseded by a sane optimistic viewpoint.

Educational campaigns of the American Society for the Control of Cancer and other agencies which instruct the public in the importance of symptoms leading to an early diagnosis have not succeeded in appreciably reducing the number of patients who continue to present themselves with well advanced cancer. In other cases the physician fails to properly evaluate early symptoms or physical signs, with the result that the cancer reaches a stage of development when little can be done to cure the case surgically and when irradiation therapy is unable to accomplish what surgery had failed to do.

The results of this have been varied. Among the public many of those who know they have cancer, or suspect that they may have it, fail to seek early surgical advice on the theory that cancer is an incurable disease.

Among physicians who are not well informed, or who have had unfortunate experiences the attitude has been similar, especially in regard to certain types of cancer, or to cancer of certain organs.

Even among surgeons one frequently hears pessimism expressed which is not justified by the facts. Especially when lymph nodes have become involved, there is an attitude of resignation which is difficult to combat. Unfortunately such lack of faith in the possibilities of radical surgery has resulted in a good deal of poor surgery. Too much reliance has been placed upon postoperative treatment with irradiation after an incomplete operation has been performed.

There are many among the public, as well as among physicians, who have lost faith in surgery without acquiring confidence in radiotherapy. This lack of confidence in either agent is today responsible for much of the chaotic condition prevailing concerning the treatment of neoplastic disease.

Education of the public, as well as of the physicians in the early symptomatology of cancer, seems to offer the best means to get cases earlier than we do. But we need more than that. We have to overcome pessimism regarding the results of treatment and instill new faith. Progress in combating cancer will never be fostered by permitting a pessimistic attitude to persist. This fact has been recognized by many and has led to cancer campaigns and publication of numerous good articles on the subject. The annual round table conference on the curability of cancer by the presentation of five year cures and other means, as instituted by the American College of Surgeons, is another attempt in this direction. However, we have to keep on presenting well substantiated facts in order to get the profession to think more optimistically about this subject.

These various considerations have influenced the writer to examine the subject in order to determine what results may reasonably be expected by radical surgery, especially in those cases in which there is involvement of the lymph nodes draining the primary tumor. It is hoped that such a presentation may help in establishing a more optimistic attitude.

One must immediately state here that enlargement of lymph nodes draining a certain cancerous area does not necessarily mean involvement. Frequently the enlargement is due to absorption of infectious material from an ulcerative lesion, rather than to invasion with cancer cells.

Enlargement of lymph nodes per se should therefore never deter one from performing a radical operation. If the primary lesion is removable, it is operable, and should be removed unless there are definite contraindications, such as distant metastases or constitutional disease. An attempt should always be made to remove the primary lesion together with the entire drainage field and its enlarged lymph nodes in one piece.

Some lesions lend themselves more to this type of radical surgery than others. Cancers of the mouth and breast, for instance, usually drain into an area which is readily accessible. Removal of the nodes with all the surrounding tissue can be accomplished without seriously interfering with other important structures or with subsequent function, and can be carried out without greatly endangering the patient.

In some other parts of the body, on the other hand, the lymphatic drainage area is not so readily accessible, and removal of the suspected or involved nodes may seriously jeopardize the circulation of adjoining structures or organs, and the operation for the removal of these nodes itself may be of such magnitude that it adds materially to a serious prognosis. In such a case, most reliance for a cure must be based on the hope that the operation is being performed before invasion of the drainage area has taken place, or one resorts to the additional use of other available agents, especially irradiation.

Many of the radical operations for cancer are undertaken without definite knowledge beforehand that nodes are actually involved. Attention was drawn above to the fact that they are frequently enlarged without being involved. On the other hand, it is a common observation that nodes are frequently involved without being palpable before operation. It is these cases which furnish a large percentage of late metastases unless they are removed. This knowledge has led to the adoption of a prophylactic lymph node extirpation as a routine procedure. On the basis of available figures it is easy to demonstrate the wisdom of such a course.

In spite of all these precautions, however, a large percentage of patients eventually succumb to their malignant disease, without having any local recurrence or without any metastases in the accessible area of invasion, which had previously been operated upon. The cause of death in such patients is distant metastases. One has to assume that they were given off by the primary tumor before its operative removal or during operation, since after operation there is no residual tumor left to provide such metastases.

Every surgeon has numerous patients who have remained well years after an operation for cancer, and there is ample evidence available in the literature that cancer under favorable conditions is curable. If the term curable is objected to, one may say that many patients remain free of disease for years after operation, perhaps for the period of their normal life, and one may, therefore, reservedly use the term cured. Several factors operate to bring about such favorable results.

(1) *An Early Diagnosis*—before cancer cells have spread by direct extension to any of the surrounding tissues or organs, by lymphatic extension to the nearest and more distant lymph nodes, or by the blood stream to distant parts of the body.

(2) *A Favorable Tumor*—meaning one which is not very cellular and which shows comparatively little tendency to metastasize, or favorable in the sense that it is radiosensitive, and that it may be destroyed by irradiation or that postoperative radiation may destroy whatever cells may have been left behind.

(3) *Radical Surgery*—One of the most important factors and one which at the present time does not seem to be sufficiently valued by many surgeons, is a radical operation performed with meticulous and painstaking care. This means understanding the most likely spread of cancer in a certain case and

operating anatomically in an attempt to get well beyond the tumor with its local extensions, as well as the complete lymphatic drainage area

It is this last factor with which this paper is chiefly concerned. Old textbooks stress the teaching "A small cancer, an extensive operation." It is one of the old truths handed down to us, and it is as true today as ever before. It seems to us that it is chiefly the influence of irradiation therapy which is responsible for the temporary neglect of old well established surgical principles.

The material used in this presentation was obtained from the records of the old Skin and Cancer Hospital, now the Skin and Cancer Unit of the New York Post-Graduate Hospital, from the literature, and from the personal records of the writer, the majority of whose cases were operated upon at Lenox Hill Hospital.

No attempt is to be made to enter into a controversy on the respective merits of surgery and radiation. The advantages claimed for radiation over surgery are ably presented by numerous writers. We do not question that excellent results are obtained with certain types of tumors and we have read with interest of the painstaking scientific work done by several of the institutions devoted to the care of cancer. However, we feel that such results are not obtained by radiotherapy in general, either due to insufficient dosage or lack of knowledge concerning the subject, or because the tumor treated is not radiosensitive. We therefore wish to present some surgical results obtained, especially in cancers which have spread beyond the primary lesion and invaded the lymph nodes. We have chosen certain well defined lesions to illustrate the point. In order to make it possible to compare our figures with those of others, we have limited them to five year results.

We shall first present a few lesions of the gastro-intestinal tract. Most of them are conceded even by radiologists to belong to the realm of general surgery. The surgical results at present are far from satisfactory, but it is hoped that with increasing knowledge of the disease, and with improved diagnostic methods, it will become possible to refer them to a surgeon earlier than has been the case in the past.

Cancer of the Rectum and Rectosigmoid—There is still no unanimity of opinion among surgeons concerning the best approach, whether to attack by the perineal route with or without a preliminary colostomy, or whether to perform a radical abdominoperineal operation in one or two stages. There is no doubt that in tumors situated low, and without lymph node involvement, a perineal operation may be carried out with greater safety in run down individuals, and with excellent results. From the standpoint of cancer surgery, however, which aims to remove the primary tumor together with the lymphatic drainage area, there is no question that the abdominoperineal operation is the preferable one. It is readily understandable, therefore, that at the present time surgeons generally are leaning toward the latter procedure.

Up to five years ago, 24 patients with carcinoma of the rectum or rectosigmoid came under our personal care, of which eight were inoperable. Table I illustrates the results obtained in this series.

TABLE I

CARCINOMA OF RECTUM AND RECTOSIGMOID (EGGERS)

Total Cases	24
Inoperable	8
Operable	16 or 66 6%
Mortality	2 or 12 5%
Five year survivors	5 or 31 2%
Still living	4 or 25%—6, 7, 10 and 13 years

None of these living patients had lymph node involvement at the time of operation, and all four were operated upon by the perineal route. It is evidently a good method for all those patients in whom the tumor has remained localized.

Because of the inaccessibility of lymph nodes situated high up, we believe that the abdominoperineal operation is the method of choice in selected cases and during the last several years we have performed it with increasing frequency. One of our patients who survived the five year period was operated upon by that method. He had lymph node involvement at the time of operation. Our other cases are too recent to warrant publication.

Rankin¹ reports operability of 76 per cent with 46 per cent lymph node involvement at the time of operation. In a series of 300 cases of posterior resection following colostomy which he studied, there was a five year cure of 34 per cent.

TABLE II

CARCINOMA OF RECTUM AND RECTOSIGMOID (RANKIN)

Total Cases	300
Operability	76%
Five year survivors	34%

This low percentage, as compared with the results of surgeons like Miles and Jones who use the abdominoperineal operation, persuaded him to adopt the latter procedure.

He quotes the following interesting figures. Miles, with an operability of approximately 30 per cent, had 79 per cent five year cures in a relatively large series of cases. Jones, with a higher operability and a similarly satisfactory mortality, had 50 per cent five year cures following his graded operation.

It seems to us that it will be difficult to obtain such results in any but carefully selected cases. With the types of patients presenting themselves to us we feel that we cannot refuse to operate upon all but 30 per cent, and our operability has, therefore, been extended to include more than twice that number. To obtain good results in such cases should be our aim, and we feel that it is possible by proper preoperative care, decompression of the bowel transfections, and an operation performed with meticulous care. We feel that in tumors situated at a high level, an abdominoperineal operation, performed in two stages, has definite advantages because it offers better

control of the blood supply, and is therefore less shocking, than a perineal operation. In addition to that it gives greater assurance of going well beyond the growth as well as the involved lymph nodes.

Cancer of the Sigmoid —Unfortunately a large percentage of patients with carcinoma of the sigmoid are admitted with symptoms of acute obstruction, while others are so far advanced that complete removal is not possible. The most ideal are naturally those without lymph node involvement. Prognosis in those patients is very good, though sometimes there are early metastases to the liver.

The Mickulicz operation is commonly employed. It is efficient when no nodes are involved and the sigmoid is long and has a wide mobile mesentery, so that one may simply bring out a loop of gut with the tumor without interfering with its blood supply. However, if the tumor is large and fixed, the mesentery short and lymph nodes involved, the operation has serious shortcomings. If one attempts to get beyond the nodes at the first stage, one may interfere with the blood supply and cause gangrene beyond the exteriorized loop, resulting in leakage and peritonitis. It has the additional disadvantage in such cases of making it practically impossible at the second stage to get beyond the nodes because of matting together of the tissues. One, therefore, may have to be satisfied with an incomplete operation. For these reasons different methods of procedure have been advised.

One may at times perform a primary resection, and in our hands this has given very good results in properly selected cases. In other cases one may effect either a cecostomy or a colostomy proximal to the tumor for decompression of the bowel, and later follow with a resection of the tumor and anastomosis of the gut. Rankin is a strong advocate of what he calls obstructive resection of the gut, after preliminary decompression.

Whatever method one chooses, it is important to resect the tumor together with the lymph nodes draining the affected portion of gut. It is a safe procedure after edema and infection have been overcome by draining and irrigating the bowel.

Rankin with his extensive experience has some very illuminating statistics concerning five year results.² He further demonstrates that the intrinsic activity of the cancer cell as measured by Broder's classification of malignancy plays an important rôle in these results.

He points out that most cancers of the colon fall into the lower grades where metastases are slower, lymph node and hepatic involvement correspondingly lower, and in consequence, the result more favorable following successful removal.

TABLE III
RESULTS IN CANCER OF THE LEFT COLON (RANKIN)

	Grade 1	Grade 2	Grade 3	Grade 4
Incidence	13%	67%	16%	4%
Five year cures	63%	51%	30%	18%

Our own experience with carcinoma of the sigmoid prior to five years ago is limited to 21 cases

Five patients, or 31.2 per cent, are living over five years, as follows 13, ten, nine, eight and six years. Two of these five, or 40 per cent, had lymph node involvement

TABLE IV
CARCINOMA OF THE SIGMOID (EGGERS)

Total Cases	21
Inoperable	5
Operable	16 or 76.3%
Five year survivors	5 or 31.2%
Two of these five,	or 40 per cent, had lymph node involvement

Cancer of the Stomach—While this article was in process of preparation, there appeared an article by Balfour³ which, on account of the enormous amount as well as the quality of its material, compels one to study it carefully. In doing so one derives inspiration and encouragement to continue in one's own limited way. Balfour's findings are based on a series of 4,793 cases of gastric carcinoma in which operation was performed in The Mayo Clinic during the period 1906-1931. In 2,112 or 45 per cent of these 4,793 cases, the growth could be removed either for palliation or in the hope of cure. In 17 per cent, gastro-enterostomy was performed, and in 38 per cent, nothing more than exploration was indicated. He states that cancer of the stomach in its early stages is so situated that in probably 90 per cent of cases the lesion could be satisfactorily removed, yet the present operability in the disease is only between 20 and 25 per cent, and further that "The curability of cancer of the stomach by surgical removal of the growth has been well established. When the growth and the regional lymph nodes can be thoroughly extirpated, five-year cures occur in about 30 per cent of cases, this is based on 18 per cent of five-year cures when lymph nodes are not involved. Such facts, in contrast to the absolute hopelessness of the disease with any other method of treatment, should constantly emphasize the importance of developing every means of recognition of the disease while the growth still can be removed."

TABLE V
CARCINOMA OF THE STOMACH (BALFOUR)

Total Cases	4,793
Resections	2,112 or 45%
Gastro enterostomy	17%
Exploratory	38%
Five year results with lymph node involvement	18%
Five year results without lymph node involvement	48%

We heartily subscribe to these views, and wish to emphasize that one should not be discouraged by the presence of enlarged nodes. So long as the tumor is removable, it should be extirpated together with all accessible

nodes Enlarged nodes do not mean that they are involved This was brought forcibly to our attention many years ago when performing one of our first resections The patient had a large palpable tumor which had been pronounced inoperable at another clinic and roentgenotherapy advised Nevertheless, the operation was performed There were enlarged nodes along the lesser and greater curvature Pathologic examination of 20 nodes showed none of them to be involved The patient lived for more than ten years and died at the age of 77

Of course the outlook with actually involved nodes is not good, nevertheless Balfour quotes 18 per cent five year cures

Our own results with cancer of the stomach have not been very encouraging, owing to extensive invasion We have extended operability to include very difficult cases which would probably have been rejected by many surgeons for a radical procedure Among 63 personal cases, in all but three of whom an exploration was done, there were 28 resections, or 44.4 per cent Of these, five died, an operative mortality of 17.9 per cent

There were 18 patients in whom resection was performed prior to five years ago Of these, six or 33.3 per cent lived five years or longer Three of these patients, or 16.7 per cent, are still living, two of them 11 years, and one five years

Only one of the six patients living five years or longer, or 16.7 per cent, had lymph node involvement

TABLE VI
CARCINOMA OF THE STOMACH (EGGERS)

Total Cases	63
Resections	28 or 44.4%
Postoperative mortality	5 or 17.9%
Five year resections	18
Lymph node involvement in	12 or 66.6%
Five year cures	6 or 33.3%
Lymph node involvement in	1 or 16.7%

These figures, though based on a small series, correspond rather closely to Balfour's figures, in regard to operability, as well as five year results Improvement is to be looked for in earlier diagnosis, proper preoperative preparation of the patient, and good surgery

Cancer of the Oral Cavity—There is available at present sufficient evidence to prove that certain primary malignant tumors of the mouth can be cured by radiation treatment On the other hand, there is available very little conclusive evidence that metastatic extensions from these tumors yield to similar radiation therapy The subject of treatment of such lesions is therefore a controversial one between radiologists and surgeons Though the primary tumors may be well taken care of by surgical means, either with an ordinary scalpel, electrosurgery, or a cautery, they may apparently be de-

stroyed with equal certainty by radium or roentgenotherapy. A surgeon in consultation with a radiologist may, therefore, select that form of treatment for the primary lesion, which offers the best chance of cure with the least amount of disfigurement or disability.

When we come to consider the drainage area in the neck, however, we are dealing with an entirely different condition. It is admitted by everyone that metastatic epidermoid carcinoma of the neck is radioresistant. Nevertheless, many radiologists use it and prefer it to a prophylactic block dissection of the neck. Although five year cures of metastatic cancer in cervical lymph nodes have been reported from a few of the large Cancer Centers, we have personally never seen a secondary cancer of the neck, definitely proved to be a cancer, cured by radiation treatment. On the other hand we have seen patients with metastatic lymph nodes of the neck cured by careful block dissection.

A discussion of this subject brings up the question whether one should be satisfied with an attempt to cure the primary mouth lesion and leave the uninvolved neck alone until manifestations of cancer develop there, or whether one should perform a prophylactic radical block dissection in order to remove unrecognized metastases. It is on this point that the radiologists and surgeons usually differ.

The former prefer prophylactic radiation over the lymph nodes of the neck in the hope of destroying cancer cells which may be present, or bringing about their incarceration by fibrous tissue. If, in spite of that a lymphatic involvement develops, they treat it with radium implantation, if small, otherwise they advise external radiation or radical surgery. Radiologists admit that implantation radiation therapy can be effective in only a very small lesion. From a surgical standpoint one may therefore ask the question why perform an operation for the implantation of radium, when a slightly more extensive operation would remove the entire focus?

The majority of surgeons, on the other hand, feel that external irradiation is ineffective in preventing or curing metastatic carcinoma of the neck. They have also found that a certain percentage of patients have metastases present in the neck even though no nodes are palpable. They, therefore, prefer a prophylactic neck dissection unless there is a definite contraindication. In case the lymph nodes are definitely enlarged, they advise and perform radical block dissections of such extent as experience has taught to be indicated.

At the Skin and Cancer Unit of the New York Post-Graduate Hospital our group of surgeons, radiologists and pathologists have made a careful study of this subject, and on the basis of established facts have formulated a policy in regard to treating the primary lesion as well as the extent of the intervention in the neck. We are definitely of the opinion that radical surgery offers the best results.

We have studied our cases over a period of years, both in regard to the direction and the extent of the lymphatic extension of different lesions. In

cancer of the lip, for instance, we have found that the extension is limited to the submental and the submaxillary lymph nodes. Extension beyond this region was found only in those cases which had palpable involvement of the upper quadrants. In the ordinary lip cases, therefore, in which neck dissection is contemplated, it is limited to the submental and submaxillary regions. It is an operation well borne, and practically without mortality. Only if the nodes of this region are definitely involved do we carry the dissection down to include the lower cervical nodes.

Kennedy,⁴ who has studied lesions of the lip, found that in patients with palpable lymph nodes, 33 per cent were involved. He further made the significant observation that among patients in whom no nodes were palpable, but in whom a prophylactic neck dissection was performed, there was actual involvement in 14 per cent. These findings furnish a strong argument in favor of routine neck dissection unless a definite contraindication exists, for it is by this procedure that 34 per cent of patients with metastases were saved.

Figi,⁵ of The Mayo Clinic, who uses the same method we have adopted, has the most striking statistics to present, which on the basis of an enormous material are more convincing than our own. His total operative mortality in 549 patients was 0.18 per cent. There was involvement of lymph nodes in 16.53 per cent. Of his patients in whom no lymph node involvement was found, 89.74 per cent lived five years or more.

TABLE VII
CANCER OF THE LIP (FIGI)

Total Cases	549
Operative Mortality	0.18%
Lymph node involvement	16.53%
Five year results with lymph node involvement	31.13%
Five year results without lymph node involvement	89.74%

In lesions of the tongue and floor of the mouth, we have found that the lymphatic invasion is much more extensive. Not alone does cancer of these organs spread to the deep cervical nodes on the affected side, but it may cross over to the other side, or by direct extension invade the supraclavicular nodes on one or both sides. Because of this, one is led to believe that the ideal procedure in cancer of the tongue should include a radical dissection of both sides of the neck. In practice one frequently has to stop short of this ideal because the patient may be old and unable to withstand these extensive procedures. One may have to be content with a neck dissection on the affected side and subsequent close observation of the other side for the possible development of late metastases.

Morrow,⁶ in a study of 98 operative cases of cancer of the tongue, found that 59 of them showed palpable nodes on admission, of which 22 or 38 per cent were bilateral. Out of 80 cases in which nodes were operated upon and examined microscopically, 38 or 47 per cent showed metastases.

Of 48 cases with palpable nodes which were examined microscopically,

23 or 48 per cent showed no metastases, of 18 cases where it was stated no nodes were palpable, seven or 39 per cent showed metastases, and out of 14 cases where the nodes were not mentioned, six or 42 per cent showed metastases. In other words, one-half of those with palpable nodes, and over one-third of the cases without palpable nodes, or where the presence or absence of nodes was not mentioned, showed involvement on microscopic examination.

TABLE VIII

CARCINOMA OF THE TONGUE (MORROW)

Total cases with lymph node extirpation	80
Total cases with lymph node involvement	38 or 47%
Five year results with lymph node involvement	11.5%
Five year results without lymph node involvement	32.4%

Of prime prognostic importance is the presence or absence of cervical metastases. Without metastases, there were 32.4 per cent five year survivals, while with metastases the five year survivals fell to 11.5 per cent.

We had 14 personal cases up to five years ago, of which one was inoperable. There were 13 radical operations with lymph node dissection. Three patients lived longer than five years, or 23.1 per cent. One of these with lymph node involvement lived nine years and died of the disease. One patient without lymph node involvement is well after ten years.

TABLE IX

CARCINOMA OF THE TONGUE (EGGERS)

Total cases with lymph node extirpation	13
Total cases with lymph node involvement	8 or 61.7%
Five year results	3 or 23.1%

One patient with involved lymph nodes lived nine years and died of the disease.

One patient without lymph node involvement is living after ten years.

Reports on cancer of the tongue from other clinics (as quoted by Morrow) are similar, whether surgery is used independently or whether surgery and radiation are combined.

There is great variation in methods of treatment, and frequently confusion arises because cases of carcinoma of the tongue are not presented separately. It is, therefore, difficult to draw definite conclusions from many of the statistics. We are under the impression that patients treated surgically suffer less than those treated with radiation. Our study has shown that the best results, both immediate and late, are obtained if one removes the primary lesion in the tongue first, or at any rate not at the same time as the nodes on the affected side. Unless contraindications exist, one should perform a complete bilateral dissection down to the clavicle.

In intra-oral carcinoma affecting other portions of the mouth, the same general surgical principles enumerated above are applied, except in certain radiosensitive or inoperable lesions, which are referred for radiation.

With the present state of our knowledge concerning intra-oral cancer, radical block dissections of the neck, performed with meticulous care, offer the patient the best chance for cure, and we believe this method of treatment should be followed unless there are definite contraindications or unless we are dealing with a very early lesion or one of low grade malignancy

Cancer of the Breast—This is one of the very common cancers and is, therefore, of tremendous interest to the public as well as to every physician. Surgically the primary tumor as well as the most common lymphatic extension, that toward the axilla, is easily accessible. One would, therefore, imagine that the disease is curable in a very large percentage of cases. Unfortunately that is not true to the degree one might wish. The reasons for this are late diagnosis, incomplete operations, extension along lymphatic paths which are not accessible to the surgeon, or blood stream invasion with distant metastases. Although attempts have been made to treat the primary disease as well as the axilla with irradiation, the results have been unsatisfactory. Consequently breast cancer is today considered to belong to the realm of surgery by most surgeons as well as radiologists.

The most recent article on the effect of preoperative irradiation in primary operable cancer of the breast by Adair,⁷ of the Memorial Hospital, represents a careful clinical as well as pathologic study of breasts removed after thorough irradiation.

Although Adair states that irradiation of the primary tumor followed by removal of the breast resulted in 48 per cent five year cures when the carcinoma was confined to the breast, he also states that it was not possible to obtain any five year cures in cases having axillary involvement. In only three of 39 cases with involved nodes was there temporary complete microscopic disappearance.

The method is beset with so many difficulties regarding diagnosis, selection of dosage, time period of treatment, method of application of irradiation and interpretation of pathologic findings, that its use in institutions with less facilities and a less experienced staff than the Memorial Hospital would be impossible. There are, in addition, distressing symptoms of pain and sleeplessness due to skin irritation, and such complications as radiation pneumonitis and anemia, which at present, at least, would discourage the use of irradiation as a routine procedure in breast cancer.

The question before us is, then, what are the results obtained with radical surgical treatment either alone or followed by irradiation? There is no doubt that at present more surgeons resort to postoperative radiation than formerly. We are under the impression that this has resulted in many incomplete operations, reliance being placed upon postoperative radiation to complete what the surgeon has failed to do. A recent paper⁸ on this subject goes so far as to advocate simple mastectomy combined with roentgenotherapy. And this in the face of Adair's carefully observed and recorded cases which show that with all the facilities of the Memorial Hospital it was not possible to

destroy axillary metastases except in a few instances. That these metastases play an important rôle in the treatment of breast cancer, as well as in the final result, is evident if one studies reported statistics on the frequency of lymph node involvement when patients are first seen (Mathews 67.3, Klingenstein 72, Harrington 64.2 [Mayo Clinic], Eggers 67.5 per cent).

If it is conceded that irradiation has little effect on them, radical surgical removal is evidently at the present time the only safe procedure. One may therefore claim for general surgery that all breast cancers with involved axillary nodes which survive be placed to its credit.

There are two excellent articles on carcinoma of the breast written by the late Frank Mathews,⁹ which we would like to recommend to every surgeon. In his first paper he reports the following figures on five year cures: 153 patients, 58 living or 37.8 per cent. Of these 58 patients, 29 had lymph node involvement. His second paper is devoted to a consideration of ten year survivors after radical operation. It contains the following interesting statistics relative to 110 patients operated upon up to ten years ago. There were 33 patients without nodes, of which 19 survived ten years or more, or 57.5 per cent; 77 patients with involved nodes, of which nine survived ten years or more, or 11.7 per cent. He reports the further interesting fact that his 28 ten year survivors were classified according to grade of malignancy, with the appended very striking result:

Grade 1	17 cases
Grade 2	8 cases
Grade 3	1 case
Not graded	2 cases
Total	28 cases

Our personal results with unselected cases of carcinoma of the breast are as follows. Up to 1932, there were seen 85 cases of breast cancer, of which five were not operated upon because of refusal or because the lesion was so extensive that it was impossible to operate in normal tissues, or because of known distant metastases. Eighty patients were operated upon by our usual radical procedure, including the removal of the breast, both pectoral muscles and the axillary contents. We consider all cases operable whenever the tumor is removable, including ulcerative lesions, bilateral involvement, and at times supraclavicular nodes, and this paper includes all such cases (Table X).

TABLE X

Total cases	85
Not operated upon	5
Operability	80 or 94.5%
Radical or incomplete operation (1 postoperative death)	80
Lived five years or longer	35 or 43.8%
Lived ten years or longer	6 or 15.0%
Of the 35 cases which lived five years or more	

Had no lymph node involvement	17 or 48 5%
Had lymph node involvement	18 or 51 5%

Of these 18 involved cases, nine or 50 per cent are still living as follows

5 years	1
6 years	1
7 years	1
8 years	2
10 years	1
16 years	2
21 years	1
	<hr/>
	9

Only one of these cases had postoperative roentgenotherapy, and one may therefore attribute the result to surgery alone

Of the total 35 cases, 21 are living at present, apparently free from disease

TABLE XI

ANALYSIS OF EIGHTY BREAST CASES OPERATED UPON
PRIOR TO FIVE YEARS AGO (EGGERS)

Five year follow up on 76 cases	95%
54 cases had lymph node involvement	67 5%
18 of these lived five years or longer	33 3%
26 cases had no lymph node involvement	32 5%
17 of these lived five years or longer	65 4%
There were 40 cases operated upon up to ten years ago	
29 had lymph node involvement	72 5%
11 had no lymph node involvement	27 5%

Of these, six or 15%, lived more than ten years, five of these are still living, of which three had lymph node involvement

TABLE XII

FIVE YEAR RESULTS IN CANCER OF THE BREAST

	Without Nodes	With Nodes	Total Cases
Klingenstein (Mt Sinai Hospital)	40%	17%	23%
White (Roosevelt Hospital)	70%	19%	35%
Sistrunk & McCarthy (Mayo Clinic)	63 9%	18 9%	36 7%
Harrington (Mayo Clinic)	71 2%	26 3%	
Mathews (St Luke's Hospital)	64 4%	19%	37 8%
		(10 years)	
Eggers (Lenox Hill Hospital)	65 4%	33 3%	43 8%

There were 80 cases operated upon up to five years ago. Four of the patients could not be followed up. We therefore report a follow up of 95 per cent. The four cases on whom there is no accurate follow up are classed as dead.

Of the total 80 cases operated upon up to five years ago, there was one postoperative death, 54 had lymph node involvement, or 67.5 per cent. Of these, 18 lived more than five years, or 33.3 per cent. This is higher than the statistics reported from most clinics. Twenty-six had no lymph node involvement, or 32.5 per cent. Of these, 17 lived more than five years, or 65.4 per cent. There were five bilateral cases in this group of 80 patients. All of them survived the five year period. Three of the patients had lymph node involvement, of which two are still living and well after nine and ten years respectively.

Several late deaths were definitely not due to metastases from the breast. One died of heart disease, another of pneumonia. There was one patient who died seven years after her breast operation, from what was diagnosed as metastases secondary to her breast carcinoma. Autopsy showed a primary carcinoma of the stomach with extensive metastases. By deducting these it is possible to present still better statistics than those quoted above.

In carcinoma affecting other organs of the body, the same general principles apply. Unless one succeeds in performing operations which include the lymphatic drainage area, good results will be obtained only in those patients in whom the lesion has remained localized. That this limits it considerably is illustrated by the different regions presented in this paper, but most effectively by the results obtained in cancer of the breast with axillary involvement.

CONCLUSIONS

As we visualize it, progress in the treatment of cancer with our present knowledge of therapy is best accomplished by an understanding of the results which may reasonably be expected in a certain case by the use of either surgery or irradiation. It is incumbent upon us to make use of that agent which our own experience as well as that of others has shown to be of greatest value. Because some surgeons have become discouraged with cancer surgery, they turn to the mystical agent of irradiation, the effects of which they know little, and hope for results. It is our feeling that the time has come to survey this entire field more carefully than has been done so far, and base sane teaching of the treatment of cancer on the facts found.

Radiation Treatment should be stressed for those lesions in which it has been found to be equally good or better than surgery. The unjustified claims of cure produced by radiation in unproven cancer should have no place in the surgical literature, as they tend to mislead the medical profession and rob patients of a chance of cure by surgical means. In the same way the claim that irradiation can cure certain types of cancer when in the experience of surgeons with an open mind such results have not been obtained should be discontinued.

It is recognized that radiotherapy is a new science, and that a great deal of necessary experimental work is being done. It is not our desire to discourage this, on the contrary, we welcome any real addition to our armamentarium in the fight against cancer. We do feel, however, that reported

results should be based on accurate scientific observation and a careful follow up in order to permit comparison with surgical results

A Combination of Radiation Treatment and Surgery or vice versa should usually not be deliberately planned in advance as a curative measure, as it tends to encourage incomplete surgery. There are of course exceptions, especially with those cancers in which it has been shown that the primary lesion yields readily to radiation treatment, while the lymphatic drainage area does not. Certain intra-oral lesions as well as carcinoma of the cervix may be cited.

It is also justified as a postoperative palliative measure, or as a curative measure in certain cases in which access to deeper portions of the tumor was found to be impossible or in which metastases were inaccessible.

Surgical Treatment should be stressed in all those lesions which by the best combined surgical experience have been found to give better results with a carefully performed operation than with other forms of treatment. It should also be employed in all those lesions in which, though they may yield to radiation, the results of treatment, as regards pain and tissue damage, are such that it leaves the patient in a worse condition than surgery does.

Emphasis should be placed on undertaking radical, painstaking surgery, with a mind on wide excision of the primary lesion as well as the anatomic distribution of the lymphatic drainage area of any given cancer.

The best way to improve our results is to train better general surgeons and so called cancer surgeons. No plea is to be made for a cancer specialist, as the number of such would not serve the purpose. Most cancers drift into the general surgical services and every surgeon must of necessity be a cancer surgeon. So called Tumor or Cancer Clinics usually deal more with visible and palpable cancer and not so much with internal cancer. Such clinics are valuable, as they offer opportunity to study cancer of different organs and usually with all known therapeutic agents. There is a danger that Cancer Clinics overemphasize radiation therapy. Nevertheless it would be of great value if more of the young general surgeons would spend a period of residency in a Cancer or Tumor Clinic or special hospital. There they would learn to evaluate the different methods and their entire attitude toward cancer would change somewhat.

An attempt has been made to show on the basis of accurate figures that radical surgical procedures offer the best chance for cure. We further believe that such results are obtained with less suffering, frequently less tissue damage and usually better function, than is possible with irradiation.

We deplore the fact that because of pessimism and lack of information concerning its true effectiveness, the finest weapon in our armamentarium is today not fully utilized by many surgeons.

On the basis of the statistics presented we wish to emphasize that cancer is a curable disease, and that early diagnosis and operation before extension into the lymphatics or the blood stream has taken place have a tremendous influence on the prognosis. But even after the lymph nodes are invaded cures are possible in a large percentage of cases by careful, meticulous surgery.

REFERENCES

- ¹ Rankin, Fred W What Can We Expect From Radical Surgery for Rectal and Recto-sigmoidal Cancer? Southern Surgeon, 5, No 3, 192-199, June, 1936
- ² Rankin, Fred W Malignant Neoplasms of the Colon New York State Jour Med, 36, No 20, 1485-1490, October 15, 1936
- ³ Balfour, Donald C Factors of Significance in the Prognosis of Cancer of the Stomach ANNALS OF SURGERY, 105, No 5, 733-740, May, 1937
- ⁴ Kennedy, Robert H Epithelioma of the Lip (With Particular Reference to Lymph-Node Metastases) ANNALS OF SURGERY, 99, No 1, 81-93, January, 1934
Ibid Epithelioma of the Lip Read by title at the Meeting of the American Surgical Association, New York City, June, 1937
- ⁵ Figi, F A Epithelioma of the Lower Lip Surg, Gynec & Obstet, 59, 810-819, 1934
- ⁶ Morrow, Albert Cancer of the Tongue ANNALS OF SURGERY, 105, No 3, 418-441, March, 1937
- ⁷ Adair, Frank The Effect of Preoperative Irradiation in Primary Operable Cancer of the Breast Am Jour Roentgenol, 35, No 3, 359-370, March, 1936
- ⁸ Grace, Edwin J, and Moitrier, William, Jr Simple Mastectomy with X-Ray in Treatment of Cancer of Breast New York State Jour Med, 36, No 9, 701-704, 1937
- ⁹ Mathews, Frank S Results of Operative Treatment of Cancer of the Breast ANNALS OF SURGERY, 96, No 5, 871-881, November, 1932
Ibid The Ten-Year Survivors of Radical Mastectomy ANNALS OF SURGERY, 98, No 4, 635-643, October, 1933
- ¹⁰ Harrington, Stuart W Carcinoma of the Breast Surg, Gynec & Obstet, 56, 438, February, 1933
- ¹¹ Klingenstein, Percy Late Results in the Operative Treatment of Carcinoma of the Breast ANNALS OF SURGERY, 96, 286, August, 1932
- ¹² White, William C Late Results of Operation for Carcinoma of the Breast ANNALS OF SURGERY, 76, 695, November, 1927
- ¹³ Sistrunk, W E, and McCarthy, W C Life Expectancy Following Radical Amputation for Carcinoma of the Breast ANNALS OF SURGERY, 75, 61, 1922

DISCUSSION OF THE PAPERS BY MR KEYNES, DOCTORS HARRINGTON,
MCKITTRICK AND EGGERS

THE PRESIDENT, DR EVARTS A GRAHAM (St Louis) Mr Keynes, we have all been held spellbound by your admirable address this afternoon. I am sure there are many who would like to express their appreciation in discussion, and perhaps to ask you some questions. I have been requested to ask you if you performed biopsies routinely in your cases.

DR MARTIN B TINKER (Ithaca, New York) A large number of Doctor Halsted's former residents and assistants are here, but they do not seem to want to talk. Thirty years ago Doctor Halsted used to say that he knew of no patient who had developed carcinoma of the breast during pregnancy or lactation that had recovered. Doctor Harrington is to be congratulated on so large a number of recoveries in such cases. Probably some of the men who worked with Doctor Halsted later may know of better results, but those reported by Doctor Harrington seem very encouraging.

The last report published from Doctor Forsell in Stockholm advised operation for cancer of the breast, and he is one of the outstanding exponents of radiation in the treatment of malignancy of all parts of the body. Some of us have to face breast operation in our own families, and we are only too glad to think that there is hope of avoiding the rather mutilating operation, as Mr Keynes has suggested today.

Relative to the presence of lymphatic nodes in the axilla. If the axilla is

dissected first, as Doctor Halsted used to do, and then we take out the contents of the axilla in connection with the whole breast. I have yet, personally to see recurrence in the axilla, either in Doctor Halsted's clinic, the work of his associates, or in my own cases. Local recurrences are extremely rare. Metastatic growths are common, unfortunately. My most frequent experience is in bones, next in the abdominal lymph nodes, and third in the chest.

DR. FREDERICK L. REICHERT (San Francisco). We have performed the radical Halsted amputation for many years, and we have studied the specimens, which include the pectoral muscles and a large area of skin. Perhaps 100 of these amputated specimens consisting of the skin, the breast tissue, the tumor and the muscles have been cleared by the Spalteholz method. Sections 2 or 3 cm. in diameter through the whole breast have been studied under binocular microscopes. In many of the fresh specimens I have injected the lymphatics with India ink. One is amazed to see the number of lymphatics that lie beneath the skin which are so close to the derma that they cannot be removed when making skin flaps. Therefore, unless one takes a large amount of skin, one does not include those lymphatics. They connect with the tumor just as the lymphatics beneath the tumor going into the pectoral muscles do, so that if interstitial radiation is used primarily, it seems to me most important not only to put these needles beneath the tumor, but also, superficially, between the tumor and the skin.

I am still quite satisfied with the radical amputation as performed starting in the axilla, and our results so far have been as good as any that I have seen reported by either radiation or a combination.

THE PRESIDENT DR. EVARTS A. GRAHAM.—Introducing Doctor Matas: I do not know how many of you realize that sitting here in the audience today is one of our most beloved members of this association, who is the only member of it who was able yesterday to note whether or not Doctor Gross's voice sounded like the real Doctor Gross. He is also the oldest living president of this Association. I am going to call upon Dr. Rudolph Matas.

DR. RUDOLPH MATAS (New Orleans). Mr. President and Fellow Members: I am rather embarrassed. To be called upon unexpectedly to speak after such a gracious introduction is no doubt quite gratifying, but no less disconcerting.

Though I am perhaps the only one here present who can claim to have heard the voice of the great founder of the American Surgical Association, I am quite sure—judging by the universal applause that yesterday greeted the president's hypothetical dialogue with Doctor Gross—his resurrection of the Master's Voice scored a perfect success.

My recollections of Doctor Gross are quite vivid, despite the half century and over that has rolled by since his visit to New Orleans as the honored guest of his devoted and most attached pupil, Dr. T. G. Richardson, Dean of the Medical Department of the University of Louisiana (now Tulane) and one of Doctor Gross' most active cooperators in the organization of this association. On this occasion Doctor Gross spoke at the commencement exercises of the Medical School. This was in 1880, and I was one of the graduating class to whom he addressed his remarks. Well do I remember his venerable figure—tall, erect and remarkably well proportioned, stately, despite the burden of the years (75), speaking without notes in a deliberate, resonant but well modulated and impressive voice. Even if one did not know of his surgical fame or of his other qualifications for greatness, the dignity of his bearing and the striking lineaments of his face, which were indicative of intellectuality and character, instantly commanded attention and respect.

Though it is long ago, I will always remember his remarks in praise of Warren Stone, the greatest hero of surgery in our section of the South. He spoke of him as a man whose heart was as big as "that of an ox," from which poured a constant stream of human sympathy and endless charity. And, it was these qualities, he said, even more than his learning and his skill, or his marvelous judgment or his incomparable wit, that made Stone the idol of the people, in life, the best loved citizen of New Orleans, and after death his loss deplored by a whole population, as a public calamity.

These reminiscent remarks I fear only serve to confirm the president's reminder of my antiquity as the oldest living president of the American Surgical Association, and perhaps justify the vanity of age which still finds enjoyment in the recognition of self in the pictures of historic events long forgotten by younger contemporaries.

Coming back to the living present, and to the "Symposium on Cancer" which has provided the day's proceedings with so much profitable discussion, I trust I may be excused if I indulge in some comments. As one who has enjoyed the privilege of Mr. Keynes' surgical clinics at "Barts" even long before the publication of his well known experience with radium in the treatment of cancer of the breast, I am well prepared to accept his statements and opinions with all the respect due to his distinguished authority. Needless to say that I am in deep sympathy with his purpose and his efforts to achieve the cure of cancer of the breast without resort to mutilating operations, and, in this aim, surely every honest surgeon shares with him the hope of its happy consummation. What is more, where is the surgeon, grown old in the warfare of surgery against cancer, who would not rejoice and shout with joy on the advent of that day when the conquest of cancer shall be announced, not as accomplished with the knife, at the operating table, and at the sacrifice of the invaded organs, but as an extinction achieved by the bloodless, painless and fundamental methods of preventive medicine and the experimental laboratory?

How much better for humanity and happier for ourselves, if the marvelous performances exhibited by contemporary surgery in the relentless pursuit of cancer—the greatest and proudest technical achievements of our Art—should no longer be necessary, except as memories of a glorious Past, just as those of us who are still able to visualize the conquest of diphtheria, 50 years ago, rejoice that we are no longer called to arms in our battles with this most malignant and formidable foe of infant life.

The present generation of surgeons, including the throat specialists, know very little, or less, of the midnight vigils, bloody tracheotomies and difficult laryngeal intubations which the great epidemics of diphtheritic croup made necessary up to the beginning of the present century. They know little of the tragic scenes and heroic episodes which made the harassed practitioners of that period dread every call to a sick child, until antitoxin and toxoid came with the conquest of diphtheria, to replace the bistoury and the tracheotomy tube.

And now, just as the tragedy of diphtheritic croup has become a fast waning memory, so do we hope that the specter of cancer may vanish with the dawn of the new day which is to bring to humanity its long hoped for deliverance, a deliverance that is to come not merely by the methods of local eradication by the knife or by radiation, whether of the roentgen or Curie type, but by the discovery of an agent capable of definitely inhibiting the growth of the cancer cell wherever it may be lodged in the organism. While there are innumerable adjunct factors, there is good reason to believe that there is essentially a single agent or factor that is responsible for the lawlessness of the cancer cells in all their polymorphous aspects. It is, therefore, not

an idle assumption of vain hope, as Doctor Morton has so well shown today that a single comprehensive cure, dealing with the cause systemically or somatically, will ultimately be attained

This symposium has been very instructive in showing *inter alia* that a certain percentage of cancers are curable by roentgenotherapy or radium, and that this curability has increased quite notably in the last five years by marked improvements in the technic of the administration of the modality employed, whether applied alone or combined with surgery. The general acceptance of Mr Coutard's methods has greatly encouraged the application of roentgenotherapy curatively and prophylactically in cancer of the breast. The number of survivals and apparent cures after radium applied by Mr Keynes technic is also a revelation. The large volume of statistics exhibited by Doctors Harrington and Eggers shows a surprisingly large number of five and ten year survivals after radical mastectomies under unfavorable prognostic conditions (axillary metastases pregnancy), all of which tends to prove that surgery, alone or combined with pre- or postoperative radiation, still holds its statistical supremacy as the method of election in the treatment of primary, early and uncomplicated malignant growths of the breast.

One of the most frequent causes for discouragement in the treatment of cancer of the breast, whether by operation or radiation, is the too frequent occurrence of metastases at a distance during the first three years after a classical radical extirpation, with a complete absence of local or regional recurrence in the field of the operation. And this will occur in tumors treated exclusively by radiation or by operation, irrespective of their small size and the early discovery of the growth.

Rising more frequently than ever is the paramount question of the choice of treatment that should be advised in dealing with a primary, clearly operable and uncomplicated malignant tumor of the breast. It would be safe to say that, until quite recently, the unanimous advice of the surgeons of the United States, in such a case, would be to operate at once, to operate as thoroughly as possible and then irradiate, systematically, to the limit of tolerance. Even now, to advise radiation without operation would be regarded by the vast majority of surgeons as a heresy or departure from orthodox practice that called for explanation.

On the other hand, the growing knowledge of the extreme variations in the radiosensitivity of tumors, especially the malignant, the increasing number of cures reported by the expert roentgenotherapists, and the notable results obtained with radium, by Mr Keynes, all tend to impair the firmness of an exclusive therapy and to bring about a closer cooperation between the surgeons and the radiotherapists of both denominations, to the end that the cancerology of the breast may profit by radiation as much, or as near, as it has benefited that of the uterus.

Finally, as an epilogue to these remarks, I would say that despite all the fallacies, defects and failures that underlie the surgical treatment of cancer of the breast, I still believe that surgery when applied, *ab initio*, with all the thoroughness and resources of modern technic, offers the best hope for the patient, especially when the operation is preceded and followed by systematic radiation applied by an expert and convinced roentgenologist.

It is understood that the treatment of cancer of the breast is now in a state of transition and that this credo is subject to change at any moment, with the discovery of the specific and real cure that expert researchers are now eagerly seeking all over the world.

DR HOWARD LILIENTHAL (New York City) In the main, I agree most heartily with Doctor Eggers. I use the roentgen ray in two ways. First, before the operation, to find out whether the patient has a lung metastasis. I do this in every breast case. This has forbidden operation in a number of cases. I consider that a very important procedure. Otherwise, I believe absolutely in what you have heard Doctor Eggers say about cancer of the breast. I employ roentgenotherapy after the operation as a prophylactic, when the wound is entirely healed.

The presence of inflammatory lymph nodes will depend on whether there is constriction of the colon. If there is constriction of the colon, a chronic disease, it is less important to take out the lymph nodes than if there are lymph nodes without constriction of the colon.

My first colon resection was performed upon a man who had a contraction produced by an adenocarcinoma of the transverse colon without infection. I was the first one to use the big Murphy button, a long, long time ago. There were numerous lymph nodes present, and I was not willing to attempt to remove them. He lived 19 years and died of another carcinoma of the same type in another part of the colon, the sigmoid flexure. Since then, I have noted especially that when there is constriction of the colon, it is less important to worry about the lymph nodes than when there is no constriction but probably ulceration.

DR LELAND S. MCKITTRICK (Boston) closing. I should only like to express my extreme gratitude to Mr. Keynes for the splendid work that he is doing, and my deep appreciation for his coming over here and telling us about it. We hope he will continue with it and if, ultimately, he can obtain better results than we can, we shall all be delighted.

MR GEOFFREY KEYNES (London, England) closing. My views have not met with a chorus of approval, and I did not expect they would. I am naturally much interested in any criticisms that may be made.

There is one important question I did not refer to, and that is relative to the proof of the disease. For some years I made a practice of doing routine biopsies before any treatment was given, or rather I removed a specimen from the tumor at the same time the needles were removed. There were no errors in those patients who were subjected to a biopsy in that way, but I found one objection. More than once there was recurrence of the disease in the small wound through which the biopsy had been made. That is to say, the cancer cells, although they were destined to disappear in the tumor, which had been irradiated, having been transplanted by the biopsy to the skin, persisted and grew again.

It was an interesting biologic experience. It showed the transplanted cells after radiation could survive, although they would disappear if left in their original position. That made me rather apprehensive of doing a biopsy by cutting into the tumor, and I have avoided it as far as possible since that time. However, as I indicated, in a great many of the patients the tumor has been removed either by local removal of the tumor or local removal of the breast, therefore, in all those patients the presence of the carcinoma has been proven.

There are a certain number in whom the diagnosis has not been proven histologically. All those patients, however, have not been seen by me alone, they have been seen by other surgeons too, and no doubt has been expressed at all as to the accuracy of the clinical diagnosis. In the vast majority, it was only too obvious.

If there is an error from neglecting biopsy, it must be, I think, very small.

I have never treated a patient in whom the diagnosis, to my mind was doubtful, that is to say, either I was clinically morally certain, or I have excised the tumor and proved it

As regards technic, the diagram which I showed you gave an indication of the usual disposition of the needles. I did not draw attention to the fact that the needles were placed in a plane deep to the mammary gland between the gland and the pectoral muscle. As a rule, the skin receives sufficient irradiation from needles placed in that plane, if they are sufficiently close together, not more than $1\frac{1}{2}$ cm apart. If they are placed parallel to one another, the field of radiation has been shown to be uniform, and a uniform field is, of course, most important in getting satisfactory results. The needles are placed in two rows, one from above and the other from below, with the points of the needles overlapping, so that if there is any difference in the intensity of the irradiation, it will be in the direction of increasing the intensity in the center where the tissue is thickest and the needles are overlapping, and beyond that it will not fall off if the needles are symmetrically and accurately disposed.

Usually, the radium reaction of the skin shows that the surface has been subjected to a satisfactory intensity of radiation. If I think the breast is too thick, or is too bulky for that to occur, then I should prefer to remove the tumor, or the breast, because as I have tried to indicate, I am advocating not wholehearted irradiation, but a compromise. I am not so convinced of the efficacy of radium that I wish to go the whole distance and say that every patient should be treated by radium alone. Far from it. And I do not at all want you to go away with the impression that I am expecting in the near future to abolish surgery in carcinoma of the breast.

The results that have been obtained, as Doctor Eggers shows, have been satisfactory up to a point. None of the statistics, however, which he quoted came very close to my survival rates, even if you allowed for a possible clinical error in diagnosis.

As regards dissection of the axilla, to which Doctor Tinker referred, and the absence of local recurrences following dissection, I agree that if the dissection is faithfully carried out, probably local recurrences will not follow. The point was, however, that there is the possibility by the dissection of the axilla of disturbing carcinoma cells which have been temporarily healed up in the neighborhood of the nodes, and that although local recurrence may not take place, yet that may adversely affect the ultimate survival rate by perhaps causing dissemination of the disease by emboli beyond the lymphatic area.

Doctor McKittrick's results are, of course, of great interest to me. His results are not altogether in agreement with mine. He found, for instance, that whenever there was residual tumor, there was active carcinoma still present. I am unable to explain the discrepancy, because in half of my residual tumors which I removed, I could find no active carcinoma cells after a most careful search. The discrepancy is rather large. It may be that I used a greater intensity of radiation.

Nowadays I seldom employ a double layer of needles, because I think the great objection is to giving an overdose to the breast, it causes considerable damage in the tissue beyond the carcinoma, and there are grave disadvantages in producing an extensive fibrosis. It is partly for that reason that I wanted to advocate a compromise between surgery and irradiation.

If I have demonstrated anything to suggest that this method is worth considering, then I have accomplished all that I hoped to achieve. It would be far too soon to upset established custom in surgical treatment, and I can only express the opinion that it appears to me the trend is toward the employment of radiation for part of the treatment, at least.

CARCINOMA OF THE BREAST
RESULTS OF SURGICAL TREATMENT WHEN THE CARCINOMA
OCCURRED IN THE COURSE OF PREGNANCY OR LACTA-
TION AND WHEN PREGNANCY OCCURRED SUBSE-
QUENT TO OPERATION (1910-1933)

STUART W. HARRINGTON, M.D.

ROCHESTER, MINN.

DIVISION OF SURGERY, THE MAYO CLINIC

MANY factors influence the prognosis and the results of surgical treatment of patients who have carcinoma of the breast. Some of the more important of these are the presence of other constitutional diseases such as diabetes, exophthalmic goiter, nephritis, *etc.*, the age of the patient, the degree of the malignancy as shown by microscopic examination of the primary lesion, the extent of the malignant involvement at the time of operation, whether the disease is unilateral or bilateral, and the thoroughness with which the radical operative procedure is carried out.

It has been recognized for many years that if carcinoma of the breast occurs when patients are pregnant or lactating, the prognosis is not good.

The purpose of this paper is twofold: (1) To show the results obtained from surgical treatment of carcinoma of the breast if the tumor occurred in the course of pregnancy or lactation, (2) to determine the results if patients had been operated upon for carcinoma of the breast and became pregnant subsequent to the operation.

Statistical studies of the results of surgical treatment of carcinoma of the breast are often misleading and it is difficult to obtain a true evaluation of the results because so many factors influence the prognosis. In order to secure an accurate evaluation of the results it is necessary that the study should include only similar groups of cases. In an attempt to determine the actual results in the various groups, I have recently made a study of all of the cases of carcinoma of the breast in which operation was performed at The Mayo Clinic from 1910 to 1933 inclusive, which comprises a series of 4,628 cases, in 4,506, or 97.1 per cent of which, the patients were traced three years or more. Of this series, in 92 cases, the tumor occurred in the course of pregnancy or lactation and operation was performed either at the time of pregnancy or lactation or soon after. The study was made of 88 patients of this group who were traced for three years or more. The second study comprises 55 patients who were operated upon for carcinoma of the breast and became pregnant subsequent to operation. All of the patients in this group were traced for three years or more. There are five additional cases which belong to both of the former groups and therefore are considered separately. In these five cases the malignancy occurred in the breast in the course of pregnancy or lactation and radical amputation of the breast was done soon afterward. All of these five patients had a subsequent pregnancy.

I should like to express my appreciation to the Division of Biometry and Medical Statistics of The Mayo Clinic for their diligence in searching for these records. The task has taken practically two years and in many instances 10 to 15 letters were necessary to trace an individual patient.

TABLE I

PERCENTAGE SURVIVAL RATES

FOUR THOUSAND, SIX HUNDRED TWENTY-EIGHT CASES OF CARCINOMA OF BREAST IN WHICH OPERATION WAS PERFORMED 1910-1933 2,952 (63.8 PER CENT) WITH AXILLARY METASTASES, 1,676 (36.2 PER CENT) WITHOUT AXILLARY METASTASES

Group	Percentage of patients traced* who lived more than indicated years after operation				
	3 yrs	5 yrs	10 yrs	15 yrs	20 yrs
Total	56.4	43.6	28.9	21.5	16.6
With axillary metastases	41.9	28.0	15.6	10.0	7.4
Without axillary metastases	82.1	72.1	53.8	42.4	32.6

* The three year percentage is based on patients traced three or more years after operation, the five year percentage on patients traced five years or more after operation, etc.

I am including a table of the general results obtained from operation in the 4,628 cases, in 4,506 of which the patients were traced three years or more, so that these results can be compared with the results obtained in the two special groups here studied. In Table I are shown the 3, 5, 10, 15 and 20 year results in cases in which operation was performed for carcinoma of the breast. In this table, as in all similar tables in this paper in which percentage survival rates are given, the rates are based in each instance on the total number of patients traced for the period referred to. For instance, the percentage 56.4, which represents the three year results in the total group of patients, is based on the total number of patients operated upon and traced three years or more. The five year percentage is based on the patients who were operated upon and traced five years or more, etc. The patients have been divided into two groups. Those who, at operation, were found to have metastases to the axillary lymph nodes and those who, at operation, were found not to have such metastases, invasion of lymph nodes at the time of operation is one of the most important indices to prognosis. It is shown in Table I that the results obtained in those cases in which lymph nodes were not involved at the time of operation were much more satisfactory than were the results in those cases in which metastases to the axillary lymph nodes had occurred.

Results When Carcinoma Occurred in the Course of Pregnancy or Lactation—Of the patients who had carcinoma of the breast associated with pregnancy or lactation, which comprise 92 of the entire series, the average age was 36.6/10 years. The first study was made to determine the percentage of patients who had, and the percentage who did not have, metastases to the axillary lymph nodes at the time of operation (Table II). This table shows that a very high percentage of patients had involved axillary lymph nodes at

the time of operation (84.8 per cent) as compared with the percentage of patients of the entire series who had similar invasion at the time of operation (63.8 per cent)

TABLE II

ANALYSIS WITH REGARD TO AXILLARY METASTASES

CARCINOMA OF BREAST IN WHICH OPERATION WAS PERFORMED, 1910-1933 NINETY-TWO CASES IN WHICH TUMOR WAS PRESENT IN COURSE OF PREGNANCY OR LACTATION

Group	Total		With Metastases		Without Metastases	
	Patients	Per Cent	Patients	Per Cent	Patients	Per Cent
Pregnant at operation	11	100	7	63.6	4	36.4
Lactating at operation	42	100	38	90.5	4	9.5
Carcinoma developed in course of pregnancy*	19	100	17	89.5	2	10.5
Carcinoma developed in course of lactation*	20	100	16	80.0	4	20.0
Totals	92	100	78	84.8	14	15.2

* Operation performed soon after pregnancy or lactation

In Table III are recorded the 3, 5, 10 and 15 year survival rates for patients who were operated upon for carcinoma of the breast which was present in the course of pregnancy or lactation. It is shown by this table that the results of operative treatment are much more satisfactory if axillary metastases were not found at operation than if such metastases were found at operation. Of this latter group no patient lived 15 years while 25 per cent of the patients without involvement of axillary nodes lived 15 years. When this table is compared with Table I it is seen that the results in the subsidiary group were much less satisfactory than those obtained in the entire series.

TABLE III

PERCENTAGE SURVIVAL RATES

NINETY-TWO CASES OF CARCINOMA OF THE BREAST IN WHICH OPERATION WAS PERFORMED, 1910-1933, TUMOR WAS PRESENT IN COURSE OF PREGNANCY OR LACTATION 78 (84.8 PER CENT) WITH AXILLARY METASTASES, 14 (15.2 PER CENT) WITHOUT AXILLARY METASTASES

Group	Percentage of patients traced* who lived more than indicated years after operation			
	3 yrs	5 yrs	10 yrs	15 yrs
Total	23.9	14.5	8.7	4.5
With axillary metastases	17.3	5.7	3.4	0
Without axillary metastases	61.5	61.5	40.0	25.0

* The three year percentage is based on patients traced three or more years after operation, the five year percentage on patients traced five years or more after operation, *etc*

A more detailed study was made of the cases in which the tumor was present in the course of pregnancy or lactation. They were divided into two main groups. Those in which there was invasion of lymph nodes at the time

of operation (Table IV) and those in which there was no such invasion at the time of operation (Table V). Each of these groups was then subdivided into four subgroups: (1) Those in which the patients were pregnant at the time of operation, (2) those in which the breast was lactating at the time of operation, (3) those in which the patient stated that the tumor developed in the course of pregnancy and the patient was operated upon later, and (4) those in which the tumor developed in the course of lactation and the patient was operated upon at a subsequent time.

TABLE IV

PERCENTAGE SURVIVAL RATES

CARCINOMA OF BREAST IN WHICH OPERATION WAS PERFORMED, 1910-1933. CASES IN WHICH TUMOR WAS PRESENT IN COURSE OF PREGNANCY OR LACTATION. SIXTY-THREE CASES WITH AXILLARY METASTASES

Subgroup	Percentage of patients traced* who lived more than indicated years after operation			
	3 yrs	5 yrs	10 yrs	15 yrs
Pregnant at operation	14.3	0	0	0
Lactating at operation	16.7	2.9	3.3	0
Tumor developed in course of pregnancy, operation later	18.8	6.2	0	0
Tumor developed in course of lactation, operation later	18.8	14.3	7.1	0
Totals	17.3	5.7	3.4	0

* The three year percentage is based on patients traced three or more years after operation, the five year percentage on patients traced five or more years after operation, etc.

In Table IV, previously referred to, are given the results obtained in the four different subgroups of those patients whose lymph nodes were invaded at the time of operation. It is shown in this table that the results of operative treatment were much less satisfactory in cases in which the tumor developed in the course of pregnancy and the patients were operated on either while the pregnancy was in progress or at a later time, than they were in those cases in which the tumor occurred in the course of lactation and the patient was operated upon at that time or at a later time. The poorest results were obtained in those cases in which the patient was pregnant at the time of operation, for of all of these patients, none lived more than five years. The best results were obtained in those cases in which the tumor developed in the course of lactation and the patients were operated upon at a subsequent time.

In Table V are given the results obtained in the four different subgroups composed of cases in which there was no invasion of lymph nodes at the time of operation. This table shows that the operative results are more satisfactory if the tumor was present in the course of pregnancy, whether the operation was performed at the time of the pregnancy or at a subsequent time. Although this group of 14 cases is small, the results are gratifying from a surgical standpoint, it is evident that surgical treatment in these cases is by no means hopeless and in fact is fairly satisfactory. It is unfortunate that this group

is not larger but it emphasizes the importance of early operation before metastases have occurred

TABLE V

PERCENTAGE SURVIVAL RATES

CARCINOMA OF BREAST IN WHICH OPERATION WAS PERFORMED, 1910-1933 CASES IN WHICH TUMOR WAS PRESENT IN COURSE OF PREGNANCY OR LACTATION FOURTEEN CASES WITHOUT AXILLARY METASTASES

Subgroup	Percentage of patients traced* who lived more than indicated years after operation			
	3 yrs	5 yrs	10 yrs	15 yrs
Pregnant at operation	75 0	75 0	66 7	50 0
Lactating at operation	33 3	33 3	0	0
Tumor developed in course of pregnancy, operation later	100 0	100 0	50 0	50 0
Tumor developed in course of lactation, operation later	50 0	50 0	33 3	0
Totals	61 5	61 5	40 0	25 0

* The three year percentage is based on patients traced three or more years after operation, the five year percentage on patients traced five or more years after operation, *etc*

Because of the poor prognosis, I have made a study to determine the grade of malignancy which was present (Table VI) This definitely shows that malignancy which occurs in the course of lactation or pregnancy tends to be of high grade and that is why such a high percentage of patients present involvement of lymph nodes at the time of operation The malignancy of none of the growths was of Grade 1 and in 59.8 per cent of the cases it was of Grade 4

TABLE VI

ANALYSIS ACCORDING TO GRADE OF MALIGNANCY

CARCINOMA OF BREAST IN WHICH OPERATION WAS PERFORMED, 1910-1933
NINETY-TWO CASES IN WHICH TUMOR WAS PRESENT IN COURSE OF PREGNANCY OR LACTATION

Group	Grade of Malignancy												Not Stated	
	Total		1		2		3		4					
	No	Per Cent	No	Per Cent	No	Per Cent	No	Per Cent	No	Per Cent	No	Per Cent		
Pregnant at operation	11	100	0	—	1	9.1	5	45.5	3	27.3	2	18.2		
Lactating at operation	42	100	0	—	1	2.4	7	16.7	29	69.0	5	11.9		
Carcinoma developed in course of preg- nancy	19	100	0	—	1	5.3	4	21.1	11	57.9	3	15.8		
Carcinoma developed in course of lacta- tion	20	100	0	—	2	10.0	4	20.0	12	60.0	2	10.0		
Totals	92	100	0	—	5	5.4	20	21.7	55	59.8	12	13.0		

The 11 patients who were pregnant at the time of operation were studied to determine if they were delivered of babies at full term or if the operation

was followed by miscarriages. It was found that six patients were delivered of live babies at full term, one patient had twins at full term and four patients had miscarriages following the operation. The four miscarriages occurred in the first two months following operation and the births occurred as follows: One in the second month, four between the third and fourth months and the twins were born five months after operation.

The cases were then studied to determine whether or not the babies were nursed from the breast while the tumor was present. In 60 cases it was definitely stated that the babies had nursed from the breast for varying periods of time and in six cases it was definitely stated that they had not. In the remaining 26 cases there was no definite statement as to whether or not the babies had nursed from the breast.

SUMMARY—Carcinoma of the breast which occurs in the course of pregnancy or lactation is usually of a high grade of malignancy, metastases to the axillary lymph nodes take place early, and the results of operation are not as satisfactory as in cases in which the tumor is not associated with pregnancy or lactation. However, operative treatment is by no means hopeless, on the contrary, results of operation are satisfactory. If the operation is performed before axillary metastases have occurred, the results are much more satisfactory than in those cases in which invasion of lymph nodes is found at the time of operation.

Results When Pregnancy Occurred After Amputation of the Breast—Because of the increasing frequency of occurrence of carcinoma of the breast in the course of the child-bearing period of life, a study was made to determine the results in cases in which amputation of the breast had been performed and the patients became pregnant subsequent to operation. Fifty-five patients between the ages of 18 and 44 gave birth subsequent to the operation. The average age of these patients was 34 $\frac{2}{10}$ years, the youngest patient was age 18 and the oldest was 43. Of this group, 27 patients had a single livebirth, ten patients had two livebirths, two patients had three livebirths, three patients had a single stillbirth, 12 patients had a single miscarriage, and one patient had two miscarriages.

A study was made to determine the interval of time from operation to the first subsequent birth (Table VII). It is shown that the shortest interval between operation and the birth of a live baby at full term was about eleven and one-half months and the longest interval was about twelve and one-half years. In 22 of the 39 patients having livebirths, the births occurred between one and three years following operation.

A study of these 55 cases was then made to determine the percentage of patients with and without axillary involvement and the number of patients represented by the four grades of malignancy (Table VIII). This study is of interest because of the high percentage (54.5) of cases in which involvement of lymph nodes was not found at the time of operation. This is higher than the percentage of cases (36.2) in which involvement of lymph nodes was not found among all cases of carcinoma of the breast in which operation was per-

formed in the same periods. This study is also of interest because of the relatively large number of patients whose carcinomata were of grades of malignancy 1 and 2. These factors indicate a more favorable prognosis than that in all cases in which operation was performed.

TABLE VII

INTERVAL FROM OPERATION TO FIRST SUBSEQUENT BIRTH

CARCINOMA OF BREAST IN WHICH OPERATION WAS PERFORMED, 1910-1933

FIFTY-FIVE PATIENTS WHO BECAME PREGNANT AFTER OPERATION

Interval	Total Patients	Live-births	Still-births	Miscarriages	Character Unknown
9-10 months					
11-12 months	1	1			
1-2 years	13	11	1	1	
2-3 years	15	11		4	
3-4 years	6	4		1	1
4-5 years	3	2		1	
5-6 years	1	1			
6-7 years	2	2			
8-9 years	2	1		1	
9-10 years	1	1			
12-13 years	1	1			
Unknown	10	4		5	1
Totals	55	39	1	13	2

TABLE VIII

GRADE OF MALIGNANCY

CARCINOMA OF BREAST IN WHICH OPERATION WAS PERFORMED, 1910-1933

FIFTY-FIVE PATIENTS WHO BECAME PREGNANT AFTER OPERATION

Group	Total	Grade of Malignancy					
		Per cent	1	2	3	4	Not Stated
Totals	55	100.0	4	8	15	11	17
With axillary metastases	25	45.5	1	2	11	9	2
Without axillary metastases	30	54.5	3	6	4	2	15

These 55 cases were then studied to determine the length of survival from the time of the operation. The series was divided into two groups: (1) Those patients who presented metastases to the axillary lymph nodes, and (2) those who did not present such metastases at the time of operation. The number of patients traced and living, as well as the percentage of cases, is given in each of the 3, 5, 10 and 15 year periods (Table IX). This was thought advisable because the percentages are often misleading when dealing with relatively small groups of cases. As is shown, the results were exceptionally good. This is a very interesting study as the results are much more satisfactory than would be expected for this group of cases. It must be understood that this is of necessity more or less a selective group of cases, because patients who have more serious types of malignant disease do not survive long enough to become pregnant subsequently, and it is evident

CANCER OF THE BREAST AND PREGNANCY

that more than half of the patients did not present axillary metastases as well as that there was a relatively high percentage of low degrees of malignancy in this group of cases. I wish to state again that this comprises all of the cases of the designated period in which it was possible to obtain information of pregnancy having occurred subsequent to operation.

TABLE IX

SURVIVAL RATES AFTER OPERATION

CARCINOMA OF BREAST IN WHICH OPERATION WAS PERFORMED, 1910-1933
FIFTY-FIVE PATIENTS WHO BECAME PREGNANT AFTER OPERATION

Group	Lived 3 or More Yrs				Lived 5 or More Yrs			Lived 10 or More Yrs			Lived 15 or More Yrs		
	Pa- tients Traced	Pa- tients	Per Cent of		Pa- tients	Per Cent of		Pa- tients	Per Cent of		Pa- tients	Per Cent of	
			Traced	Pa- tients		Traced	Pa- tients		Traced	Pa- tients		Traced	Pa- tients
			Traced	Traced		Traced	Traced		Traced	Traced		Traced	Traced
Totals	55	52	94.5	53	42	79.2	37	28	75.7	21	15	71.4	
With axillary metastases	25	22	88.0	23	13	56.5	12	6	50.0	5	3	60.0	
Without axil- lary meta- stases	30	30	100.0	30	29	96.7	25	22	88.0	16	12	75.0	

These 55 cases were then studied to determine the length of survival after the first birth following operation. Of the 55 cases, in 45 the time of the subsequent birth was definitely determined. In ten cases it was known that birth had occurred subsequent to operation but it was impossible to determine the exact time of the birth, therefore these cases cannot be included in the record of survivals. Because of the relatively small number of cases it was thought best to tabulate this group under traced patients and patients living in the different periods. The results of this study are shown in Table X.

TABLE X

SURVIVAL AFTER FIRST BIRTH SUBSEQUENT TO OPERATION

CARCINOMA OF BREAST IN WHICH OPERATION WAS PERFORMED, 1910-1933
FIFTY-FIVE PATIENTS WHO BECAME PREGNANT AFTER OPERATION

TWENTY-FIVE WITH AXILLARY METASTASES, THIRTY WITHOUT AXILLARY METASTASES

Group	Intervals after First Birth Subsequent to Operation											
	1 Yr. or More		2 or More		3 or More		5 or More		10 or More		15 or More	
	Traced	Lived	Traced	Lived	Traced	Lived	Traced	Lived	Traced	Lived	Traced	Lived
Totals	45	41	44	34	41	30	37	28	22	14	14	8
With axillary metastases	21	17	20	12	17	8	14	8	4	2	4	1
Without axillary metastases	24	24	24	22	24	22	23	20	18	12	10	7

This table shows that of the 45 patients mentioned, who were operated upon for carcinoma of the breast and who gave birth subsequently, 41 survived one year or more after the birth, and of the 14 patients who had given birth 15 or more years previous to the time of inquiry eight had survived.

The preceding tabulation (Table X), applying to the entire group of 55

cases, includes 42 patients who had had babies at full term and 13 patients who had had miscarriages. A study was then made of the 42 patients who had babies only at full term. Of these 42 patients, 39 had live babies and three had stillbirths. It was found that 19 or 45.2 per cent of these patients had axillary metastases at the time of operation and 23, or 54.8 per cent, had no such metastases at the time of operation. Of the 42 patients, 37 were definitely traced, 12 patients stated that they had nursed the baby, seven did not nurse from the breast and in 18 cases definite information on this point was not obtained.

TABLE XI

SURVIVAL AFTER FIRST BIRTH SUBSEQUENT TO OPERATION

CARCINOMA OF BREAST IN WHICH OPERATION WAS PERFORMED, 1910-1933

FORTY-TWO PATIENTS WHO WERE DELIVERED AT FULL TERM AFTER OPERATION

NINETEEN WITH AXILLARY METASTASES, TWENTY-THREE WITHOUT AXILLARY METASTASES

Group	Intervals after First Birth Subsequent to Operation											
	1 Yr or More		2 or More		3 or More		5 or More		10 or More		15 or More	
	Traced	Lived	Traced	Lived	Traced	Lived	Traced	Lived	Traced	Lived	Traced	Lived
Totals	37	33	37	29	35	26	31	24	18	12	12	7
With axillary metastases	16	12	16	10	14	7	11	7	3	2	3	1
Without axillary metastases	21	21	21	19	21	19	20	17	15	10	9	6

In Table XI are given the survivals from one to 15 or more years after the birth of a baby at full term by patients who previously had undergone amputation for carcinoma of the breast between the years 1910 and 1933. Tables X and XI differ in that Table XI excludes miscarriages. This table shows that of the 37 traced patients, 33 lived one or more years after the birth of the baby and of the 12 patients who had had live babies 15 or more years previously, seven were living 15 or more years after the birth of the baby. These results are surprisingly good. The chief value of this study is to establish the fact that patients who have been operated upon for malignant disease of the breast can survive the birth of a child for 15 years or more, in fact one of these patients lived 20 years. This study in no way establishes what the results of operation would have been if the pregnancy had not occurred, as this can be determined only by comparing similar groups of patients who have survived in the different age periods and have not had a subsequent pregnancy. This comparative study is being made and will be of interest as this group of cases becomes larger.

Five Cases Which Presented Features of Both of the Foregoing Groups—

The following five cases I have segregated into a separate group, inasmuch as they belong in both of the preceding groups and could not be included in either one separately. The group is so small that it is difficult to summarize, therefore, I am here presenting a brief report, in abstract, of each of the five cases. They are of interest because of the long survival of some of the patients who had many pregnancies, in all of these cases the carcinoma of the breast was present in the course of the pregnancy and all of the patients had one or more pregnancies subsequent to the operation.

CASE REPORTS

Case 1—The patient was 31 years of age. The tumor was noted in the course of lactation and three and one-half months later the patient underwent radical amputation of the breast. She had a subsequent livebirth four years and nine months after operation, she lived ten and three-fourths years after operation and six years after birth of the child.

Case 2—The patient was 34 years of age. The tumor of the breast was noted one month after she had weaned the child. Radical amputation was performed six weeks later. Nine months after operation the patient had the first livebirth and two years and eight months after operation she had a second livebirth. Ten months after birth of the second child, radical amputation of the remaining breast was effected. The patient's duration of life was nine and one-half years dating from the first operation and five years dating from the second operation.

Case 3—The patient was 30 years of age. The tumor was noted in the course of lactation. Radical amputation was performed two and one-half months after she had weaned the child. The patient had a livebirth one year and nine months after operation. The mother is living four and one-half years after operation.

Case 4—The patient was 31 years of age. The tumor was noted in the course of pregnancy, two years before radical amputation of breast. A second pregnancy occurred after operation, the character of this subsequent pregnancy could not be determined. The patient died about the time of the second birth, one year and nine months after operation.

Case 5—The patient was 28 years of age. The tumor was noted in the course of pregnancy. Local excision of the tumor was performed in the course of the pregnancy and the patient had a miscarriage at eight months. Radical amputation of the breast was performed at the clinic one month after the miscarriage. She then had one subsequent miscarriage and one subsequent livebirth. The patient died about the time of the birth.

SUMMARY—A complete study has been made of all of the cases of carcinoma of the breast in which operation was performed at The Mayo Clinic between 1910 and 1933. Of this entire group special studies were made on two series of cases: (1) Cases in which the malignancy was present in the course of lactation or pregnancy, and (2) cases in which pregnancy occurred subsequent to radical amputation of the breast.

The first special study was made on a group of 92 cases, to determine the results of operative treatment and it was found that the results of operation in these cases were not as satisfactory as they were in the entire series of cases in which operation was performed from 1910 to 1933. The results indicate that the condition is by no means hopeless and in those cases in which invasion of lymph nodes had not occurred at the time of operation, the results were satisfactory.

The second special study was made in a group of 55 cases. The 3, 5, 10 and 15 year survivals from the time of operation were determined. The survivals following the birth of the first baby were determined from one to 15 years after the birth of the baby. Of the 37 patients of the second series, who were traced, 33 lived one or more years after the birth of the baby and of 12 patients whose babies were born 15 years or more before the time of the inquiry, seven had survived. This group is of particular interest because it establishes the fact that patients can survive many years following childbirth and may have as many as three births following operation for carcinoma of the breast. The operative results in this group were satisfactory and the

final results were found to be more satisfactory than those of the entire series. It is difficult, and may be hazardous, to draw any definite conclusions from this study other than what has been stated above, namely, that it is possible for patients to bear children following radical amputation of the breast and to live for many years without recurrence of carcinoma of the breast. However, I do not believe that it should be inferred from this study that pregnancies subsequent to radical amputation may not be followed by metastatic malignancy because it must be remembered that these cases in reality constitute a selected group, inasmuch as all patients who give birth to children at full term must have survived operation approximately a year and usually patients who survive so long are in good general condition, which eliminates many of the patients whose malignancy is of high grade. This unintentional selectivity increases by necessity as the interval increases from the time of operation. Although the results in this series were far better than it was expected they would be, we shall continue to advise young women who are in the child-bearing period of life not to have subsequent pregnancies. It is gratifying, however, to know that if pregnancy does develop subsequent to radical amputation, the patient may give birth to babies at full term and that metastatic malignancy may not develop as a consequence. In these cases the prognosis is probably more favorable if the patient does not nurse the baby.

RESECTION WITH ASEPTIC END-TO-END ANASTOMOSIS FOR CARCINOMA OF THE COLON

WILLIAM F. MACFEE, M.D.

NEW YORK, N. Y.

FROM THE DEPARTMENT OF SURGERY OF THE NEW YORK HOSPITAL AND CORNELL MEDICAL COLLEGE AND THE
SURGICAL SERVICES OF ST. LUKE'S HOSPITAL, NEW YORK, N. Y.

IN THE long period which preceded the introduction of antiseptics and asepsis, intestinal surgery of any kind was seldom undertaken. Attention in this direction was confined almost entirely to the treatment of open intestinal wounds. In the management of these it was observed that there was a tendency of peritoneal surfaces to adhere to each other when brought into contact. This principle was sometimes made use of by bringing the visceral peritoneum about an open intestinal wound into contact with the parietal peritoneum about the corresponding wound of the abdominal wall so that union between visceral and parietal peritoneum was established. In this way the discharge of intestinal contents was led to the outside and eventual healing of the fistula sometimes took place.

It occurred to Antoine Lembert¹ that the same principle might be applied to bring about the direct healing of intestinal wounds and, in 1826, he published an article in which he described such healing secured by the approximation of the peritoneal coats of the opposing wound edges. The approximation was brought about by the use of the type of suture which today bears his name.

With the introduction of asepsis and the beginning of modern surgery, about 1885, a marked impetus was given to abdominal surgery, and with increasing confidence attacks were made upon abdominal conditions which had hitherto been largely neglected. In this category was carcinoma of the colon.

Reports on the surgical treatment of isolated cases or on a few cases of this disease now began to appear and by the beginning of the present century von Koerte,² Czerny,³ de Bovis,⁴ and von Mikulicz⁵ were ready to report the results of surgical treatment in a considerable number of cases.

The prevailing procedure at that time was that of resection of the involved segment of colon with immediate restoration of continuity by suture. The results of this treatment in the words of Mikulicz left much to be desired. The general mortality ranged between 30 and 50 per cent, the greatest single factor being general peritonitis.

Already efforts were being made to find a safer way of operating upon such cases and Mikulicz gives Oscar Bloch,⁶ of Copenhagen, credit for being the first to apply the principle of exteriorization in the treatment of carcinoma of the colon. In 1892, Bloch brought a freely movable sigmoid lesion with its mesenteric attachment out of the abdominal wall and incised the intestine above the site of the tumor.

In 1895, F. T. Paul⁷ of Liverpool described two operations, one performed

in 1894 and the other in 1895, in which the tumor bearing portion of the colon was brought out of the abdominal wound and resected. Glass intestinal drainage tubes were tied into each end and the two ends of bowel were attached side by side to bring about the formation of a spur. The spur in each case was later broken down with a suitable crushing instrument. In the first case the remaining fistula was closed by extraperitoneal suture and remained healed. The second case died about two weeks after crushing of the spur. Autopsy showed no trouble at the site of resection, the patient having apparently died of uremia.

In 1903, von Mikulicz reported the results in 16 cases treated by the procedure which bears his name, a procedure which had been employed in his clinic for the preceding five years. In principle and purpose it is very similar to the operations previously described by Bloch and Paul. Mikulicz, however, made a point of excising the mesentery along with the segment of bowel in order to include the regional lymph nodes. In the 16 cases reported from Mikulicz's clinic there were two deaths, a mortality of 12.5 per cent, as compared with a mortality of 42.9 per cent in 21 cases from the same clinic treated by resection with primary suture. He stated in his description of the operation that in the beginning he allowed the tumor to remain 12 to 48 hours before actual removal, but that it had become his practice as a rule, to remove the tumor immediately after closing the abdominal wound. Mikulicz did not maintain that his procedure should be carried out in all cases. It is interesting that he regarded tumors of the cecum as borderline cases.

The results reported by Mikulicz from the exteriorization procedure were far better than those of any operation known at that time. It was generally accepted as a definite improvement in the surgical treatment of colonic cancer and soon gained a popularity which largely holds to the present time. Numerous slight alterations have been introduced, notably the obstructive modification of Rankin,⁸ but the operation remains essentially unchanged.

As time passed, however, a certain amount of dissatisfaction with the operation arose. The colostomy, even though temporary, was a feature quite disagreeable to the patient and sometimes considerable difficulty was encountered in closing the stoma. Exteriorization of the involved segment of colon often proved difficult, especially in corpulent patients with a short mesentery. Furthermore, the operation was found not to be entirely free from the complications it sought to avoid.

It occurred to a number of investigators that resection with immediate anastomosis would be far preferable if only some means of avoiding the hazard of peritonitis could be found. The question of avoiding peritonitis resolved itself into the problem of finding a way to resect a segment of bowel and restore continuity without contamination from the intestinal contents. This obviously would be possible if the closed ends of intestine could be sutured together end-to-end and the resulting diaphragm in some way thereafter obliterated.

This problem engaged the serious attention of Halsted,⁹ who devised

interesting experimental methods of aseptic anastomosis, but he does not record that they were applied clinically. O'Hara,¹⁰ in 1901, devised a means of suture over two special clamps which were integrated by a third serrefine clamp, which held the cauterized ends of the intestine together during suture. After one clamp had been removed and before the final suture was tied, the second clamp, before withdrawal, was passed into proximal and distal ends of the intestine to break down the diaphragm. This maneuver appears to have compromised the asepsis.

In 1907 Rostowzew¹¹ devised a special crushing clamp, the heavy blades of which were equipped with a second pair of narrow blades. These could be locked and remained on the ends of the intestine until the suturing was virtually complete. They were then withdrawn and the final sutures tied. Continuity of lumen was restored by invaginating the wall of the intestine with the finger through the circular anastomosis.

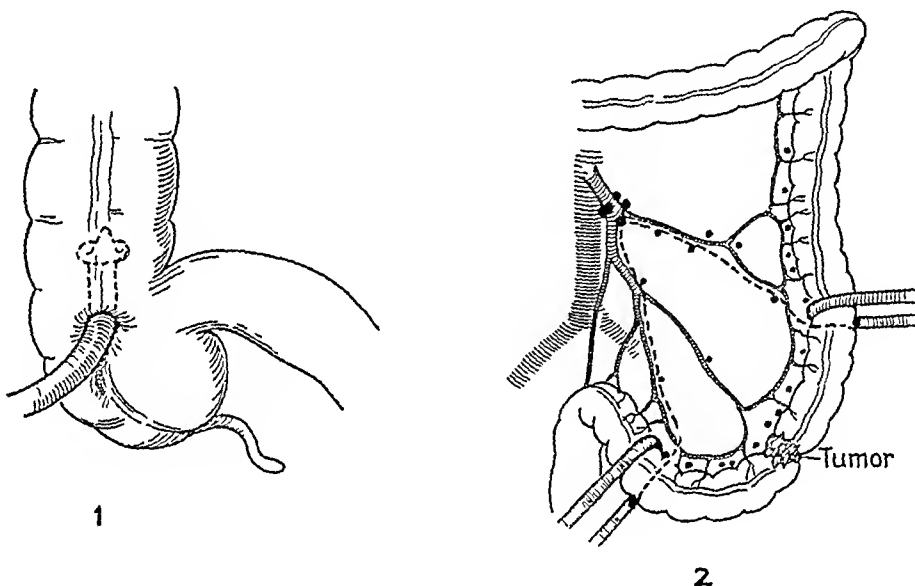


FIG 1—Large mushroom catheter introduced into cecum for decompression and lavage in cases of partial or complete obstruction.

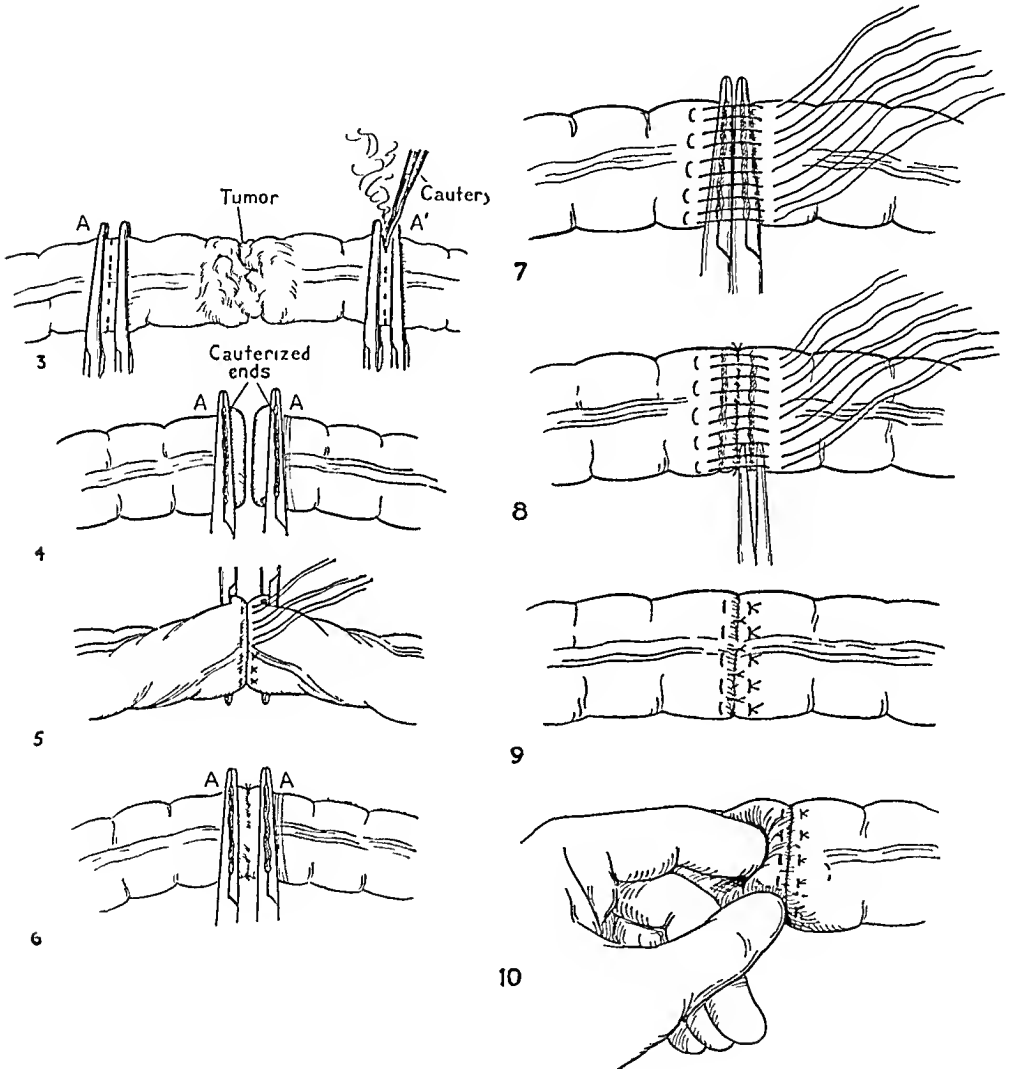
FIG 2—Shows pieces of rubber tubing used for light traction during mobilization of a segment of colon. Diagrammatic outline of mesentery to be removed is indicated by dotted line.

Parker and Keir,¹² in 1908, described the use of an inverting suture, called a basting stitch, which they used to close temporarily each of the opposing ends of intestine while anastomosis was performed with a continuous inverting suture. The basting stitches were afterward withdrawn. The method was again brought to attention by Kerl¹³ in 1923.

Methods of anastomosis with or without the aid of special clamps have been described by Rankin,¹⁴ Schoemaker,¹⁵ Collins,¹⁶ Fraser and Dott,¹⁷ Pringle,¹⁸ Furniss¹⁹ and others, but no simpler or more satisfactory method has been advocated than that of suture over ordinary Kocher clamps as presented by Scarf.²⁰

The accompanying illustrations, which follow closely the method described by Scarf, bring out nothing new in aseptic intestinal anastomosis and are simply intended as a review of a practical method.

Figure 1 shows a cecostomy with the introduction of a large mushroom type of catheter. This provides a means of deflating a colon distended because of partial or complete obstruction. By copious daily lavages with warm water over a period of two or three weeks the colon may be restored to approximately a normal state. Resection by eventration procedure or with immediate anastomosis may then be undertaken with far greater safety. Lockhart-Mummery,²¹ who reports excellent results with end-to-end anastomosis, em-



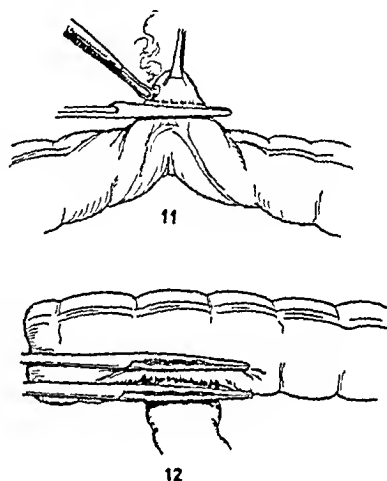
FIGS 3 TO 10—Indicate steps in resection with aseptic anastomosis over clamps. In practice the sutures are placed as near as possible to the clamps to avoid turning in a wide cuff.

phasizes the importance of this preliminary procedure. In lesions beyond the midtransverse colon, a right transverse colostomy serves admirably for the same purpose. It is fortunate that obstruction of any considerable degree is not often associated with lesions of the cecum. When present it may be overcome by ileotransverse colostomy or in severe cases by simple ileostomy.

performed high enough to avoid interference with a possible subsequent resection

Carcinoma situated in any part of the colon distal to the hepatic flexure may be resected according to the procedures illustrated in Figs 3 to 10, which require little elucidation. Lesions of the rectosigmoid junction may often be removed in the same way. Tumors of the rectum must, as a rule, be removed by other methods of procedure

Malignant lesions of the cecum, ascending colon, and hepatic flexure are usually treated by resection of the right colon with ileotransverse colostomy. Figs 11 and 12 illustrate the method of performing ileocolostomy by suture over clamps. Fig 11 shows an opening being made in the side of the colon to receive the end of ileum. Fig 12 shows the end of ileum approximated to side of colon with the posterior suture completed. The anterior suturing is conducted as shown in Figs 7, 8 and 9. The same procedure may be carried out as a side-to-side ileocolostomy. After removal of the elevated cone of large bowel wall (Fig 11), it is important to inspect the piece removed in order to be sure of patency after the anastomosis is completed. Ileocolostomy may be performed as a palliative procedure, as the first step in a two stage resection of the right colon, or as part of a one stage resection.



Figs 11 and 12—Show primary steps in application of same procedure to ileocolostomy

There are certain points with regard to resection with immediate anastomosis which warrant serious attention

(1) The segment to be resected should not be clamped immediately. If this is done, there is a tendency to use the clamps as retractors and accidental tearing may occur. Furthermore, there is a disinclination to change the sites primarily selected for division and anastomosis once the clamps have been applied. There is also some risk of a leak at the points which were first crushed. Sometimes, however, during the freeing of the mesentery the circulation is compromised beyond the points anticipated. Disregard of this fact may lead to failure of healing.

It is a good practice to use pieces of rubber tubing as retractors (Fig 2) during mobilization of the bowel. The clamps are then applied as the last step preliminary to resection and are placed at points where there is no question as to adequacy of circulation. As an additional means of insuring blood supply, Parker and Kerr and Lockhart-Mummery²² advise cutting across the intestine at an angle of 45 degrees from the mesenteric toward the anti-mesenteric border, in such a way that a length of antimesenteric border greater than mesenteric border is removed. They believe this measure gives further assurance of a good blood supply at the point of anastomosis farthest from the mesentery where experience has shown most failures of union occur. It provides also a wider lumen at the line of anastomosis. One must agree with

Lockhart-Mummery that the real reason why axial union of the large intestine fails has little to do with the nature of the intestinal contents but is due entirely to the blood supply of its walls. Unimpaired blood supply is a matter of the first importance.

(2) There must be no inclusion of fat or bleeding vessels between the approximated serous surfaces at the line of anastomosis. The collections of fat must be carefully dissected away from the occluding clamps and the small vessels secured, preferably with mosquito clamps, and ligated with fine material.

(3) Each suture should include in its hold a bit of the submucous layer of intestine which Halsted²³ has shown to be so important in the security of intestinal sutures.

(4) There must be no undue tension on the approximating clamps or on the subsequent suture line.

(5) Immediate resection with anastomosis should never be undertaken in the presence of any degree of obstruction. Edematous gut holds sutures poorly and it is far safer to perform a decompressing operation first and wait until the proximal colon returns to normal before attempting resection. This is usually a matter of two or three weeks.

(6) The operation should be conducted with as little trauma as possible, especially with regard to peritoneal surfaces. It is to be remembered that the so-called aseptic anastomoses are seldom truly aseptic. Cultures taken from the suture line have usually shown a growth of organisms. In one case a culture of *C. welchii* was obtained. The patient, however, made an entirely uneventful recovery, showing at no time evidence of active infection. In another case a man with carcinoma of the transverse colon had in addition an inguinal hernia for which he had been wearing a truss. Following resection of the tumor he developed a colon bacillus infection with pus formation in the hernial sac. There was no evidence of peritoneal involvement elsewhere. It is entirely conceivable that this localized infection was due to the dissemination of bacteria into a peritoneal sac which had been damaged by the truss. A culture taken from the suture line showed organisms of the type found in the sac.

Injured peritoneum like partially devitalized tissue elsewhere is susceptible to infection. On the other hand, intact peritoneum is relatively resistant. Infection in the fat of the abdominal wound without peritoneal involvement is a common occurrence in abdominal operations associated with slight contamination. When there is a choice, therefore, of leaving the anastomosis intra- or extraperitoneal, as in low sigmoid lesions, it is usually safer to place it within the peritoneal cavity.

With consistent observation of these principles of operative conduct, resection with end-to-end anastomosis may be relied upon to give satisfactory results. It is obvious, too, that the basic considerations are much the same regardless of the type of operation.

The purpose of the following study was to determine as far as possible the status of resection with aseptic anastomosis as compared with other pro-

cedures employed in the surgical treatment of cancer of the colon. Theoretic considerations can be accepted only insofar as they are borne out by practical application, and it was to apply the clinical test that a review of consecutive cases was undertaken.

The total number of 318 cases comprises 100 from the records of New York Hospital since 1932, and 218 from St. Luke's Hospital since the latter part of 1929. Since resection with aseptic anastomosis was not often undertaken in either institution prior to the dates given, it seemed futile to go farther back. The classification of tumors as to location is based primarily upon the surgical problems involved rather than upon anatomic considerations.

The question of operability so far as anticipation of a cure is concerned is frequently a difficult one to decide from the records. In some cases radical removal was performed as a palliative measure. It seemed more satisfactory on the whole to divide the cases into two main divisions: those in which the tumor was removed, and those in which the tumor was not removed. The main divisions were then further arranged according to the type of surgical treatment carried out. Deaths occurring in the hospital were regarded as operative deaths regardless of the apparent cause.

TABLE I
SUMMARY OF CASES REVIEWED

	Cecum, Ascend- ing Colon, Hepatic Flexure	Trans- verse Colon	Splenic Flexure, Descend- ing Colon	Sigmoid	Recto- sigmoid	Total	Per Cent
Number of cases reviewed	78	22	50	130	38	318	
Number of cases in which tumor was removed	39	11	30	68	7	156	49.1
Number of cases in which tumor was not removed	39	11	20	62	31	162	50.9

Comment—Table I is interesting because it indicates that the tumor could be, or at least that it was, removed in only 49.1 per cent of the cases admitted to the hospitals. The need of improvement in early diagnosis is obvious.

Table II records the results of the exteriorization procedure of Bloch, Paul, or Mikulicz, as one chooses. The operation performed in virtually all cases was obstructive resection. The general mortality in this group was 27.9 per cent. It will be observed that the most favorable results were obtained in cases of carcinoma of the sigmoid. Lesions of the right colon gave the least favorable results, with a mortality of 50 per cent. The group is small and not to be taken as proof. It indicates, however, that application of the Mikulicz procedure in tumors of the right colon as advocated by Lahey²⁴ is not without danger in other hands.

TABLE II

TUMOR REMOVED BY EXTERIORIZATION PROCEDURE, PAUL-MIKULICZ

	Cecum, Ascend- ing Colon, Hepatic Flexure	Trans- verse Colon	Splenic Flexure, Descend- ing Colon	Sigmoid	Recto- sigmoid	Total	Per Cent
Number of Cases	10	4	18	35	1	68	
Died in hospital	5		7	7		19	27 9
Died subsequently of cancer			4	10	1	15	22 1
Complications							
Operative soiling			4	3		7	10 3
Wound infection	2		2	3		7	10 3
Abscess or local perito- nitis	1		2	1		4	5 9
General peritonitis			5	3		8	11 8
Postoperative obstruc- tion	1		1			2	2 9
Evisceration			1			1	1 5
Lymph Nodes Involved							
Histologically	3	1	2	11		17	25 0
Living 1 yr							
Living 2 yrs							
Living 3 yrs							
Living 4 yrs		1		2		3	4 4
Living 5 yrs or more						0	
Lymph Nodes "Not In- volved" or Not Men- tioned in Report	7	3	16	24	1	51	75 0
Living 1 yr				2		2	2 9
Living 2 yrs	1			4		5	7 4
Living 3 yrs			2	3		5	7 4
Living 4 yrs							
Living 5 yrs or more	2		2	2		6	8 8

A review of the causes of death in the individual cases of Table II is to some degree instructive

(1) Female, age 40 Died of a purulent peritonitis There was a spontaneous or induced rupture of the cecum at the site of the tumor

(2) Female, age 55 Died of general peritonitis, cause not obvious Tumor was in the sigmoid

(3) Male, age 71 Tumor in sigmoid, cause of death not stated

(4) Female, age 55 Perforating tumor of descending colon infiltrating the retro-peritoneal tissues Spilling of feces occurred during the operation and death was due to peritonitis

(5) Female, age 70 Obstructive resection for carcinoma of the ascending colon and cholecystectomy for gallstones were effected at one operation The cause of death, which occurred two days later, was not definitely ascertained

CARCINOMA OF THE COLON

- (6) Male, age 56 Tumor of sigmoid complicated by abscess The patient died four days after obstructive resection from general peritonitis, C welchii
- (7) Male, age 84 Sigmoid tumor Death was thought to be due to embolism
- (8) Male, age 58 Died suddenly with cyanosis and dyspnea one day after obstructive resection of a carcinoma of the ascending colon
- (9) Male, age 70 Died of circulatory failure two days after obstructive resection of a sigmoid tumor
- (10) Male, age 61 Died 11 days after obstructive resection of the right colon, from localized peritonitis and paralytic ileus
- (11) Female, age 63 Died of wound infection and pleuritic effusion after a Mikulicz resection of a tumor in splenic flexure
- (12) Male, age 65 Died of general peritonitis following removal of a tumor of the splenic flexure complicated by perforation

TABLE III

TUMOR REMOVED BY RESECTION WITH ASEPTIC END-TO-END ANASTOMOSIS

	Cecum, Ascend- ing Colon, Hepatic Flexure	Trans- verse Colon	Splenic Flexure, Descend- ing Colon	Sigmoid	Recto- sigmoid	Total	Per Cent
Number of Cases	15	3	12	21	5	56	
Died in hospital	3	1	1	3	1	9	16 1
Died subsequently of cancer	4		3	4	2	13	23 2
Complications							
Operative soiling	1		1	1	1	4	7 1
Wound infection	3	1	1	2	2	9	16 1
Abscess or local perito- nitis	1		1			2	3 6
General peritonitis	2		1			3	5 4
Postoperative obstruc- tion	1					1	1 8
Evisceration					1	1	1 8
Lymph Nodes Histologi- cally Involved	5	1	4	8	2	20	35 7
Living 1 yr	1		1	1	1	4	7 1
Living 2 yrs	2			1	1	4	7 1
Living 3 yrs		1		1		2	3 6
Living 4 yrs							
Living 5 yrs or more	1					1	1 8
Lymph Nodes "Not In- volved" or Not Men- tioned in Report	10	2	8	13	3	36	64 3
Living 1 yr	2			1		3	5 4
Living 2 yrs			2	4		6	10 7
Living 3 yrs			2		1	3	5 4
Living 4 yrs							
Living 5 yrs or more							

(13) Female, age 50 Died following obstructive resection of the sigmoid complicated by adherent small intestine Cause of death either obstruction or peritonitis

(14) Male, age 47 Obstructive Mikulicz resection performed for carcinoma of the cecum with intussusception Died 17 days later of secondary obstruction

(15) Male, age 67 Accidental gross fecal contamination occurred during removal of a carcinoma of the sigmoid Death caused by gangrenous infection of abdominal wound, C welchii, and local peritonitis

(16) Male, age 55 In this case, of carcinoma of descending colon, difficulty was experienced in bringing the obstructing clamps completely out onto the abdominal wall The ends of intestine retracted into the abdominal cavity and a partial evisceration occurred Death was apparently due to peritonitis

(17) Female, age 66 Bowel accidentally opened during mobilization of descending colon, death caused by peritonitis

(18) Female, age 73 Death followed closure of colostomy stoma 11 weeks after obstructive resection of carcinoma at the splenic flexure Autopsy revealed obstruction due to angulation of the colon at site of closure

It is obvious in retrospect that errors in judgment and technic contributed in some cases to the fatal outcome

Table III shows the results of resection with aseptic end-to-end anastomosis When ileocolostomy was performed, it was usually aseptic end-to-side In some cases special clamps were used but generally the suturing was done over Kocher clamps The mortality from all causes was 16.1 per cent

It will be seen that the incidence of wound infection in this series was high In one case it led to evisceration and the death of the patient Attention to this aspect of aseptic anastomosis should lead to improvement In a few of the more recent cases hexylresorcinol solution has been used to flush the wound after closure of the peritoneum Wound infection has not occurred in these cases, but they are too small in number to be significant

In the group treated by resection with aseptic anastomosis the causes of death were as follows

(1) Male, age 52 Died of bronchopneumonia 11 days after resection of a carcinoma of the sigmoid There were no abdominal complications

(2) Male, age 63 Died of lobar pneumonia seven days after resection of a carcinoma of the transverse colon There were no abdominal complications

(3) Female, age 71 Died ten days after resection of a carcinoma at the recto-sigmoid preceded by a cecostomy with suitable time interval An abdominal wound infection followed resection and there was a separation down to the peritoneum On the seventh postoperative day the patient sneezed or coughed violently and evisceration through the infected wound occurred Death from general peritonitis followed three days later

(4) Female, age 66, obese Resection of the right colon for a carcinoma at the hepatic flexure A small abscess was entered during mobilization of the tumor The patient died eight days after operation with a severe abdominal wound infection and general peritonitis There was no gross leak at the site of the end-to-side ileocolostomy but healing was defective

(5) Female, age 80 Died three days after resection of a carcinoma of the sigmoid A preliminary cecostomy had been done Death was recorded as being due to shock, ileus, and cardiac failure

(6) Female, age 60 Died three days after a one stage resection of the right colon with end-to-side ileocolostomy Autopsy revealed a local peritonitis without leak at the

CARCINOMA OF THE COLON

anastomosis and without obstruction The patient was described before operation as being in poor condition There had been marked loss of weight with exhaustion from protracted vomiting and diarrhea

(7) Female, age 70 Died nine days after a one stage resection of the right colon for a carcinoma of the cecum with end-to-end ileocolostomy A leak occurred at the line of anastomosis with the development of a local peritonitis, obstruction of the ileum, and an abdominal wound infection At a second operation the ends of the intestine were exteriorized The patient died of a general peritonitis

(8) Male, age 65 Died two days after a one stage resection of a carcinoma of the sigmoid Death was preceded by hiccough, vomiting, diaphoresis, and edematous breathing A definite cause of death was not established

(9) Female, age 68 Died 15 days after a one stage resection of a carcinoma of the descending colon with partial obstruction End-to-end anastomosis was undertaken with the aid of a Furniss clamp A leak from the proximal segment occurred during the anastomosis and the aseptic procedure was abandoned The operation was concluded with an exteriorization of the ends of the colon Death was associated with clinical evidence of a general peritonitis Autopsy was not obtained

TABLE IV
TUMOR REMOVED BY OPEN RESECTION

	Cecum, Ascend- ing Colon, Hepatic Flexure	Trans- verse Colon	Splenic Flexure, Descend- ing Colon	Sigmoid	Recto- sigmoid	Total	Per Cent
Number of Cases	14	5	2	8	3	32	
Died in hospital	3	1	1	1		6	18.8
Died subsequently of cancer	3	3		3		7	21.9
Complications							
Operative soiling	14	5	2	8	3	32	100.0
Wound infection	4			1		5	15.6
Abscess or local perito- nitis	1			1		2	6.3
General peritonitis	1		1			2	6.3
Postoperative obstruc- tion	1					1	3.1
Evisceration						0	
Lymph Nodes Histologi- cally Involved	4	3	1	4		12	37.5
Living 1 yr							
Living 2 yrs							
Living 3 yrs							
Living 4 yrs				1		1	3.1
Living 5 yrs or more						0	
Lymph Nodes "Not In- volved" or Not Men- tioned in Report	10	2	1	4	3	20	62.5
Living 1 yr							
Living 2 yrs	1					1	3.1
Living 3 yrs	2			1		3	9.4
Living 4 yrs							
Living 5 yrs or more	2					2	6.3

In this group also certain errors of judgment and technic contributed to the mortality. In some cases, undertaken in one stage, it appears that a two stage procedure would have been safer.

Table IV records the results following resection with open anastomosis. It includes all resections in which an open anastomosis was performed at any stage of the procedure. It consists mainly of resections of the right colon in which an open ileocolostomy has been effected, and of tube resections for carcinoma in the sigmoid region.

The operative mortality in this group was 18.8 per cent. In one case the cause of death was not definitely ascertained, in all others it was directly connected with the operation, the most common cause being peritonitis.

Table V lists all cases in which the tumor was not removed. It includes 99 cases upon whom a palliative operation, usually colostomy or entero-enterostomy, was performed, 32 cases who had an exploration only, and 31 cases who were not operated upon. The hospital mortality following palliative operations was 45.5 per cent, and that following exploration only was 37.5 per cent. Of the patients who had no operation, 32.3 per cent died in the hospital. It is unfortunate that it is so frequently impossible to determine operability without exploration.

TABLE V
TUMOR NOT REMOVED

	Cecum, Ascend- ing Colon, Hepatic Flexure	Trans- verse Colon	Splenic Flexure, Descend- ing Colon	Sigmoid	Recto- sigmoid	Total	Per Cent
Palliative Operations							
Cecostomy, colostomy, or enteroenterostomy	22	6	12	40	19	99	
Died in hospital	9	3	7	20	6	45	45.5
Simple Exploration	8	3	3	12	6	32	
Died in hospital	3	1	2	6		12	37.5
No Operation	9	2	4	10	6	31	
Died in hospital	3	1	2	4		10	32.3

The incidence of lymph node involvement and the follow up record of the patients who survived operation are contained in the tables. The majority of patients have been operated upon too recently to provide anything of much value in the way of ultimate results.

SUMMARY

A review of 318 consecutive, recent cases of carcinoma of the colon is presented. Carcinoma of the rectum was excluded. In 156 cases the primary tumor was removed and in the remaining 162 cases it was not removed.

The primary purpose of the review was to determine the relative safety of the surgical procedures most commonly employed in the extirpation of cancer of the colon

In 68 cases removal of the tumor was accomplished by a Paul-Mikulicz procedure, usually with the obstructive modification. The operative (hospital) mortality was 27.9 per cent, all causes included.

In 56 cases resection with immediate aseptic end-to-end or end-to-side anastomosis was carried out. The operative, or hospital, mortality in this group from all causes was 16.1 per cent.

The comparative mortality between the group treated by the Paul-Mikulicz operation and the group treated by resection with aseptic end-to-end anastomosis appears to favor the latter procedure and in this agrees with Wilkie's²⁵ report.

In 32 cases the tumor was resected and the open ends of intestine were united by suture. Gross leakage during the procedure was prevented by suitable clamps. The mortality in this group was 18.8 per cent.

In 99 cases subjected to palliative procedures, the hospital mortality was 45.5 per cent, and in 32 cases who had simple exploration, the hospital mortality was 37.5 per cent. Of 31 patients who had no operation, 32.3 per cent died in the hospital.

This review provides further evidence that an unsatisfactory state exists in regard to the early diagnosis and successful treatment of cancer of the colon. Of 318 patients admitted to the hospital, 162 were inoperable from the outset and 34 died following resection of the tumor. Only 122 or 38.4 per cent left the hospital with any chance of survival. Of this number, 35, or an additional 11 per cent, are known to have succumbed to cancer. The number of possible survivors at the end of a relatively short period is therefore reduced to 27.4 per cent of those originally admitted for treatment.

REFERENCES

- ¹ Lembert, A. Memoire sur l'enterorrhaphie, avec la description d'un procede nouveau pour pratiquer cette operation chirurgicale. Repertoire general d'anatomie et de physiologie pathologique et de clinique chirurgicale, 2, 100-107, Paris, 1826.
- ² Koerte, W. von. Erfahrungen uber die operative Behandlung der malignen Dickdarmgeschwulste. Verhandlung der deutsche Gesellschaft fur Chirurgie, 29, No. 2, 61-120, Berlin, 1900.
- ³ Czerny, V., und Rindfleisch, W. Operationen am Magen und Darm. Beitrage zur klinische Chirurgie, 9, 661-803, 1892.
- ⁴ Bovis, R. de. Le cancer du gros intestin, rectum excepté. Rev. de Chir., 22, 528-553, 677-714, Paris, 1900.
- ⁵ Mikulicz, J. von. Chirurgische Erfahrungen uber das Darmcarcinom. Klinische Chirurgie (Langenbeck), 69, 28-47, 1903, Small Contributions to the Surgery of the Intestinal Tract. Boston Med and Surg Jour., 148, 608-611, 1903.
- ⁶ Bloch, Oscar. Om extra-abdominal Behandling af Cancer intestinalis. Nordiskt Medicinskt Arkiv, 24, 1-41, 1892.
- ⁷ Paul, F. T. Colectomy. Brit Med Jour., 1, 1136-1139, May 25, 1895.

- ⁸ Rankin, F W Resection and Obstruction of the Colon (Obstructive Resection) Surg, Gynec & Obstet, 50, 594-598, 1930
- ⁹ Halsted, W S End-to-end Suture of the Intestine by a Bulkhead Method Trans Amer Surg Assoc, 28, 256-261, Philadelphia, 1910, Surgical Papers 1, 233-237, Baltimore, Johns Hopkins Press, 1924, A Bulkhead Suture of the Intestine Jour Exper Med, 15, 216-224, 1912, Surgical Papers 1, 238-245, Blind-End Circular Suture of the Intestine, Closed Ends Abutted and the Double Diaphragm Punctured with a Knife Introduced per Rectum ANNALS OF SURGERY, 37, 356-364, 1922, Surgical Papers 1, 249-258, 1924
- ¹⁰ O'Hara, M, Jr A Method of Performing Anastomosis of Hollow Viscera by a New Instrument ANNALS OF SURGERY, 33, 179-184, 1901
- ¹¹ Rostowzew, M Iw Aseptische Darmaht Arch f klin Chir, 82, 462-485, Berlin, 1907
- ¹² Parker, E M, and Kerr, H H Intestinal Anastomosis without Open Incisions by Means of Basting Stitches Johns Hopkins Hosp Bull, 19, 132-137, 1908
- ¹³ Kerr, H H The Development of Intestinal Surgery J A M A, 81, 641-647, August 25, 1923
- ¹⁴ Rankin, F W Operative Procedures The Colon, Rectum, and Anus 714-812, Philadelphia, W B Saunders & Co, 1932
- ¹⁵ Schoemaker, J Some Technical Points in Abdominal Surgery Surg, Gynec & Obstet, 33, 591-596, December, 1921
- ¹⁶ Collins, F K Aseptic Resection of Intestine ANNALS OF SURGERY, 76, 739-744, 1922
- ¹⁷ Fraser, J, and Dott, N Aseptic Intestinal Anastomosis With Special Reference to Colectomy Brit Jour Surg, 11, 439-454, 1923-1924
- ¹⁸ Pringle, S Aseptic Resection of the Intestine Brit Jour Surg, 12, 238-243, 1924-1925
- ¹⁹ Furniss, H D A New Method of Intestinal Anastomosis Transactions of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, 47, 26-31 1934
- ²⁰ Scarf, J E Aseptic End-to-end Suture of Intestine ANNALS OF SURGERY, 83, 490-495, 1926
- ²¹ Lockhart-Mummery, J P Diseases of the Rectum and Colon 2nd Ed, 566-567, Baltimore, William Wood and Company, 1934
- ²² Lockhart-Mummery, J P End-to-end Anastomosis of the Colon Surg, Gynec & Obstet, 24, 247-250, 1917
- ²³ Halsted, W S Circular Suture of the Intestine An Experimental Study Am Jour Med Sci, 94, 436-461, 1887, Surgical Papers 1, 185-211, Baltimore, Johns Hopkins Press, 1924
- ²⁴ Lahey, F H Carcinoma of the Colon Am Jour Surg, New Series, 22, 64-73, 1933, Resection of the Right Colon and Anastomosis of the Ileum to the Transverse Colon after the Plan of Mikulicz Surg, Gynec & Obstet, 54, 923-929, June, 1932
- ²⁵ Wilkie, P D P Cancer of the Colon Its Surgical Treatment Lancet, 1, 65-68, January 13, 1934

THE DEVELOPMENT OF LABORATORY SERVICE IN A CANCER HOSPITAL

JAMES EWING, M D

NEW YORK, N Y

FROM THE MEMORIAL HOSPITAL, NEW YORK, N Y

It is interesting to compare the laboratory study of tumors in the 1890's with the service now available in a cancer hospital. One may not depreciate the efficiency or scope of histologic diagnosis of tumors in that comparatively early period. The main descriptive history of the major forms of cancer had been written before that time and were abundantly employed by surgeon and pathologist. The benign character of giant cell tumors, first stated by Warren, in 1828, had been fully elaborated by Nelaton, in 1866, but was generally ignored. About 1905, I had the pleasure of cutting the pages of Nelaton's monograph in the library of the New York Academy of Medicine. Virchow's *Geschwulste* left little to be said about the clinical features and structure of the benign tumors. In 1888, Hellman gave a full report of 83 cases of soft part sarcomata, including the so called fascial sarcomata, and noted their bad prognosis. Anatomic studies had laid the basis for the radical breast amputation and emphasized, probably over-emphasized, the necessity of removing muscle and much skin. Between 1860 and 1882, a series of contributions from Kolliker to Recklinghausen left only certain refinements of classification for later students of neurosarcoma. Paltauf, in 1896, described most of the outstanding characters of the lymphosarcoma group. Pel and Ebstein wrote about acute Hodgkin's disease in 1887. Golgi introduced the term endothelioma for the dual psammoma in 1869, after which the scope of this group of tumors rapidly expanded, leading to controversies not yet ended. The description of Kaposi's disease dates from 1869. The discussion of gastric ulcerocancer began with Rokitansky in 1840, continued actively through 1890 with Hauser's important critical study and remains today a favorite field of theorizing and debate. In the 90's it was rather acute. Malassez traced the origin of adamantinoma in 1885. The salivary gland tumors were minutely described and their clinical course traced, especially by French authors from Duplay,¹ in 1875, Poncet,² in 1888, to Collet,³ in 1895, while Volkmann⁴ presented his mistaken thesis on their endothelial origin in 1895. Definite understanding of renal tumors dates from 1883 when Weichselbaum and Greenish described the common adenomata, and Grawitz identified the adrenal rest tumors. In 1892, Birch-Hirschfeld introduced the term hypernephroma. Wilms completed his monograph on embryonal renal tumors in 1899. In thyroid tumors there was an extensive literature when Kocher⁵ wrote in 1899.

The experimental transplantation of lower animal tumors was pursued

actively after 1876 when Novinsky transferred the infectious lymphosarcoma of dogs. Hanau and von Eiselsberg transferred successfully malignant tumors in lower animals, and, in 1894, Moreau reported a completely successful study of a transplantable mouse carcinoma, but the lack of notice paid to this pioneer work is said to have led to the suicide of the author. Many abortive efforts were being made to find a constitutional remedy for cancer, the most prominent of which was probably thyroid extract which had considerable popularity in the 80's.

Accordingly, when one entered the field of tumor diagnosis at that time he readily learned about the main groups, but he found himself lost in a complicated mass of little known varieties and subvarieties of structure and considered himself fortunate if he could vaguely surmise the position of any but the more common types of structure. An extensive, rapidly increasing and often controversial literature added to the confusion. While the basis of the modern theory of cell autonomy had been laid by Cohnheim, Thiersch, Wilms, and Ribbert, and was uniformly accepted by pathologists, the parasitic theory was enjoying its highest popularity and occupied a dominating place in cancer research. There was little inducement to pursue the special etiology of any group of tumors and rather less opportunity.

Probably the main handicap to progress was the scanty supply of material. Cancer cases found their way uniformly into all the general hospitals and no clinic in America, and few in Europe, made any effort to collect large numbers of cases of any one type. In order to gain a comprehensive review of any group of tumors, one had to travel around to many laboratories, and content himself as a rule with a miscellaneous collection of unclassified cases, generally without clinical data, which left him more confused than ever.

Another handicap was the scarcity of early cases, which seemed to be a universal condition, for Ribbert, about 1904, said that no one had ever seen the beginnings of mammary cancer. Verse⁶ published his observations on 12 early gastric cancers discovered at autopsy in 1908. It was not until the introduction of radiologic diagnosis that early gastric and many early internal cancers began to be available for study.

The chief difficulty lay in conditions which offered no inducement and little opportunity for anyone to devote himself intensively to the study of cancer, and there was no center where one could obtain substantial instruction in this field. Tumor diagnosis was a mere incident, interesting enough, in the routine of the general pathologist, and cancer treatment was an irksome, and mostly gloomy, chapter in the busy life of the general surgeon. Hansemann was the outstanding figure in the German clinics, but when, in 1895, I undertook to take a course of instruction under him, the reception was none too cordial, and my notes of the course refer mainly to his erroneous view that hypernephroma was of endothelial origin.

At the beginning of the twentieth century, the final demonstration by Jensen and Loeb, of the ready transplantability of certain lower animal

tumors, laid the basis for the modern cancer research laboratory. This subject occupied the Giatwick Laboratory at Buffalo under Gaylord, and the Frankfort Institute under Ehrlich. The Imperial Cancer Research Laboratory of London, founded mainly for this purpose under Bashford, gave impetus to many potential institutions in Europe and America. The first International Cancer Congress, in 1905, was called mainly to discuss these problems. The experimental cancer research laboratory was now fully under way.

Soon the problems arising in the therapeutic use of radium and the roentgen ray thrust themselves upon the notice of the cancer laboratory and added great stimulus and wider scope to the work, and heavily to the expenses of organization. The material resources placed at the disposal of these laboratories were from the outset rather liberal and for the time adequate.

Most important was the impetus given by the experimental and laboratory activities upon the few cancer hospitals then existing, upon the cancer services in general hospitals, and upon the medical profession. A new era of great promise was dawning and preparations were rapidly made to take advantage of the new opportunities. One notes especially the important contributions that began to appear from the London Cancer Hospital, the Middlesex Hospital, the Czerny Institute of Heidelberg, the Buffalo Laboratory, and from many less known institutions and clinics in Europe and America. The final and most important development was the creation of several special cancer hospitals and institutes, combining clinical and laboratory studies, gathering larger numbers of cancer patients in one place, and leading to much greater specialization in all departments. Beginning about 1910 and continuing in spite of the Great War, special cancer institutes and hospitals were built in Stockholm, Paris, Milan, Rome, Lisbon, Madrid, Buenos Aires, London, Manchester and New York, and reorganization of the cancer service was effected in a great many large general hospitals in all parts of the world. The fact that this radical change proceeded rapidly, often cutting across existing organizations, causing much inconvenience and some confusion, and arousing opposition from many quarters, is perhaps the best proof of its wisdom and necessity. On the whole, these revolutionary innovations which carried endorsement of specialization in the study and treatment of cancer were received with remarkable hospitality. Such, in brief, is the history of the development of the modern cancer institute and laboratory. From experience in one laboratory of this type and visits to others, it is possible to compare the character of the service rendered with that available 40 years ago.

To the descriptive tumor pathologist, one of the chief advantages of the large cancer hospital is the wealth of material. The cases are numerous enough to permit the frequent use of the method of diagnosis of obscure cases by comparing transitional cases of the same general group. Diagnosis by transitional cases is well illustrated by an experience with the group of

intermuscular myxosarcomata These tumors were long known as "fascial sarcomas," but their histogenesis was obscure I had been seeing these rather rare tumors for many years and had never been satisfied that they arose from the fasciae, while their relation to other tumors of the same regions was quite undetermined However, during the past several years, encountering a greatly increased number of such growths, it became apparent from transitional cases, that the so called fascial sarcoma is a form of liposarcoma producing mucus instead of fat, and sometimes containing in the same tumor areas of fetal liposarcoma and myxosarcoma This method of diagnosis by transitional cases is about the only resource available for the identification of many obscure structural types, and it is effective only when a large material is available It is particularly important in the group of neurogenic tumors, and the lymphomata, but often proves of decisive value in many other groups

The great value of abundant material and transitional cases was really first brought into prominence by Codman, when, in 1916, he established the Registry of Bone Sarcoma The value of this large collection immediately became so obvious that several other registries were soon established and there are now at least seven extensive tumor registries located at the Army Medical Museum

The diagnosis of tumors by aspiration has been practiced for many years It was used by Mixter 25 years ago, and later by Guthrie, especially for lymph nodes The routine use of this method to replace the surgical biopsy was first brought into prominence by the work of Martin and Ellis When the method was discussed not long ago before the American Association for Cancer Research, it was generally rejected Yet an experience of five years with several thousand cases has established the aspiration biopsy as an extremely important and very reliable method under the conditions existing in a large cancer hospital Its safe use requires instruction of the operator, continued experience with the technic, knowledge of the sources of error, and experience and patience on the part of the pathologist The technic varies and must be learned for each organ Under other conditions the method may not be recommended Yet the most extensive atlas of aspiration tumor material comes from Pavlowsky of the General Surgical Clinic at Buenos Aires

The significance of variations in grade of malignancy of tumors was well known in 1895, but estimates of prognosis were based on the general features of the cases rather than on strictly histologic signs It remained for Broders to point out the practical value of prognoses based solely on careful histologic analysis of tumor structure He worked with a large material This type of laboratory report is now generally accepted as essential for the information of the surgeon However, one still hears many objections against the grading of tumors The same tumor may contain several structural types The great majority of tumors of one kind are much alike, and the prognosis depends more on the extent of the disease

and the character of the treatment than upon histologic features. It is true that when one deals with a small number of cases, he may find that all fall within the intermediate grades which carry an average prognosis, but with a large material many cases begin to appear in the extreme grades where the prognosis is distinctly affected by the potential malignancy as measured alone by histologic structure. The grading of tumors has, therefore, become an established practice with tumor pathologists. Personally, while always considering the ordinary signs of malignancy, I prefer to rely, where possible, on certain peculiar structural features which have become recognized as determining prognosis, such as the favorable outlook for mammary cancer composed exclusively of clear cells, as mentioned by Delbet, the very fatal tendencies of mammary cancer with complete loss of polarity and isolation of cells, the good prognosis of lymphosarcoma containing many large clear cells, and the remarkable relation between prognosis and fibrillar content of ocular melanoma described by Callender and Wilder.⁷ All these and many other specific histologic characters of tumors have been brought to light by workers who had access to an extensive material.

Estimation of the degree of radiosensitivity is another problem which belongs to the special cancer laboratory. While the general principles of radiosensitivity were early recognized and formulated, increasing experience soon showed that the response to radiation is subject to so many variable factors that its estimation becomes a broad clinical problem. In fact the exceptions observed to theoretic rules and principles are so numerous and capricious that the tumor pathologist falls back largely upon actual experience before venturing to predict what any tumor will do under radiation. Who would anticipate that a carcinoma of the pharyngeal wall would react better than an identical structure on the mucosa of the cheek, that while primary thyroid tumors are generally resistant, yet excellent results are obtainable with residual masses left after partial excision, that thymus tumors disappearing rapidly after treatment persistently recur unless treatment is long maintained, that embryonal carcinoma of the testis yields completely and permanently, while a slight adenocarcinomatous structure in a testis tumor renders that structure resistant? These and scores of other peculiarities can be learned only by experience with an extensive material over a long period, and it is difficult to see how one can make much progress in this field under any other conditions. No doubt principles of radiosensitivity will gradually emerge and bring some order in this difficult and essential field of tumor diagnosis. Already we are finding that radical changes in the intensity and spacing of dosage and size of portals bring unexpected results not heretofore observed, so that the whole approach to the problem of radiation therapy is steadily altering. It has now become essentially a problem for clinical judgment and the exercise of a genuine detective sense.

There is another type of service which cannot well be rendered except in a large clinic and laboratory where special types of cases are concen-

tiated in one service. A distinguished American pathologist recently made a valuable report on the fate of about 300 cases of tumors of the salivary glands with complete follow up. This extensive material was carefully analyzed from many angles and the following conclusions drawn:

Recurrence was observed in 23.23 per cent. Endeavors to correlate the structure with the clinical behavior totally failed. The data collected did not indicate that roentgenotherapy or radium is of any greater value than the knife. Convincing figures were given to show the importance of not operating until the tumor reaches the size of a lemon. A review of this report indicates that the main conclusions drawn were justified. No data on the dosage of radiation were given and the use of the expression that the patients were "exposed" to the roentgen ray or radium suggests that the treatment was mostly of a miscellaneous type, and certainly did not meet modern standards. However, when one compares these conclusions with those held in large cancer hospitals, such as the Radiumhemmet at Stockholm or the Memorial Hospital, New York, all the conclusions are contradicted. These clinics find a notable, although not invariable relation between cellular structure and rate of growth, surgical curability, and radiosensitivity. The recurrences are far less than 23.23 per cent, and radiation is employed successfully in certain cases. These clinics operate immediately and would not venture to wait until the tumor reaches the size of a lemon. How is it possible that such divergent opinions can be reached regarding a common type of tumor? The reason appears clearly when it is found that the report cited refers to 300 cases coming from 90 different operators, while in the special cancer hospitals the material is under the charge of one service or one man. If 300 cases are distributed among 90 operators over a period of 20 years, how long will it take the 90 operators to become familiar with the peculiarities of parotid tumors?

Several years ago Bloodgood circulated among a group of recognized general pathologists, a series of cases of borderline lesions of the breast. There was a wide difference of opinion regarding the true nature and clinical significance of these lesions. This situation disclosed the fact that many of the pathologists and the clinics they served did not have enough experience with such lesions to determine positively their practical significance and that statistics regarding the cures of mammary cancer in such clinics were of doubtful value.

Recently Cole submitted eight early lesions of the stomach, which he had diagnosed as cancer, to 21 recognized pathologists. The result was surprising and significant, for opinions were about equally divided as to the malignancy of these lesions. The fact that Cole did not always submit all the material for examination at the same time added a humorous element to the inquiry, but did not alter its significance. It was shown that one or two sections were inadequate to form the basis of an opinion in such cases, and that several sections of the whole lesion were required. It was also emphasized that the recognition of early gastric cancer may be a very dif-

ficult undertaking requiring wide experience in general and tumor pathology, and it seems necessary to admit that many general pathologists are not familiar with the significance of certain early neoplastic changes in the stomach. Here again it was demonstrated that statistics regarding the curability of any but the well established and readily recognizable cancers of the stomach in American clinics are of doubtful value. From my personal knowledge of European clinics, I feel that similar conditions exist abroad.

There is no reason why the highest standards of efficiency in histologic diagnosis, combined with complete follow up, should not be developed in surgical clinics of general hospitals, provided they have a large material, but these conditions seem more readily attainable in a cancer hospital where pathologists and clinicians are not absorbed in other subjects. That such facilities do not exist in all hospitals is indicated by the experience of Bloodgood and Cole, and by the Codman Registry of Bone Sarcoma.

Science Service in a Cancer Hospital—The distinguished director of research of a great industrial company voices the feeling of science editors and directors of industrial research in general, when he expresses his fear that cancer research is not well organized, lacks cooperation, and would be much improved if under the control of highly competent coordinators. He has a "hunch" that local elevations of temperature may be responsible for the outbreak of many cancers, and he refers to the probable importance of Langmuir's observations on molecular surface films and surface tension of cells in the control of cell growth and malignancy, and he asks where can he take these ideas to have them tried out. The answer is that he can take them to any well organized cancer institute in this country or abroad, secure reference to the literature on these subjects, and get a competent opinion as to whether they are worth while pursuing, but rarely will he find the elaborate organization or extensive resources required to cover every phase of such investigations, or anything approaching the facilities of the industrial research laboratory.

Nevertheless, in the laboratory organization of the cancer institute, and hospital, one finds departments representing the fundamental sciences, all of which are necessary for the proper functioning of the institute. These include physics, biophysics, chemistry, biology, physiology, each with its own quarters, equipment, budget and staff.

Physics—The department of physics carries a substantial routine service in installing, repairing and calibrating roentgen ray machines, designing and constructing instruments with the aid of a staff of mechanics, filling prescriptions for radon, and learning how to avoid the hazards of the work. The staff of physicists are in constant demand for consultations with the clinical staff regarding the calculation of surface and depth dosage, the effects of different filters, the influence of changes in the size of portals, and of variations in the spacing of doses, and a great variety of theoretic questions on which they are presumed to base opinions on experimental

data Without such control, radiation therapy becomes an inefficient and rather dangerous routine practice, and lacks the refinements which modern standards demand The physics department, cooperating with biophysics, is largely a research department investigating by experimental methods the significance of intensity, voltage, amperage, and wavelength of radium and roentgen rays, the effects of secondary radiation in different media, the nature of secondary effects on patients, the chemical changes produced in simple substrates, the chemical and physiologic effects on growth and functions of plant and animal indicators Most of our knowledge of radio-physiology has emanated from the laboratories of cancer institutes In the educational field the physics department gives lectures and demonstrations and some formal courses of instruction for students, physicians and physicists It should be the aim of such a department to provide an adequate career in physics as a science to those who enter the service, but its first responsibility is to furnish essential aid to surgeon and radiologist in the treatment of patients

Chemistry—It is difficult to know how to organize and keep within reasonable limits the chemical department of a cancer hospital The routine clinical services practice medical chemistry on the usual liberal scale of a general hospital, and add numerous special requests which occupy the time of one or more competent chemists There is an endless series of small chemical investigations which make a strong appeal to the research instinct and therefore form the bulk of chemical cancer literature There are chemical sides to nearly every cancer problem, so that chemical apparatus is required in all the hospital laboratory divisions The search for growth stimulating and inhibiting substances, cancerigenic agents, metabolic products, the elusive cancer diagnostic tests, specific nutrient media, composition of tumor tissue, chemotherapy, organotherapy, are some of the many topics which occupy the main attention of many modern cancer laboratory staffs These problems seem to make the most effective appeal to those who undertake to establish cancer research on limited resources, which as a rule were better assigned to the support of good routine service to patients Chemical fields are now so highly specialized that well trained workers in many departments are demanded if significant results are to be obtained A review of current chemical cancer literature indicates that much labor would be eliminated if chemical problems were under the direction of one who is familiar with cancer, but under any circumstances, a strong chemical department is a foundation stone of a good cancer service organization

Biology—The department of biology deals with the experimental production of tumors and with genetics Each of these fields may be pursued in institutions devoted exclusively to research, and generally exhaust the resources of such institutions, but I believe that each would receive invaluable support, suggestions and control from the atmosphere of a large cancer hospital with the constant flow of problems arising in the cancer patient Soluble problems of cancer genesis have usually been suggested by observa-

tion on cancer in the human being, and the progress of knowledge of the causation of mammary, uterine, gastric, bladder and cutaneous cancer may be cited in support of this view. Cancer genetics especially stands to profit by closer contact with human cancer. In either field the services of highly competent biologists are required.

Oncologic Physiology—During recent years there has been an increasing realization of the significance of tumors as aberrant organs exerting a definite and often profound influence on the body as a whole, and even in some instances resulting from a disturbance of the altruistic relations of the organs, especially those with internal secretions. The long established physiologic effects of thyroid, ovarian, adrenal and parathyroid tumors called attention to the physiologic principle years ago, and the recent demonstration of the estrogenic action of coal tar derivatives has been a strong stimulus to physiologic studies. Endocrinology has been full of pitfalls and so the initial enthusiastic assumptions that estrogenic agents are actually operative in the origin of certain tumors and that the demonstration of such agents in various tumor tissues proved that the tumors were caused thereby, have not been confirmed. Estrogenic substances are found in onion tips and are widely distributed in nature. Agents giving the reactions of intermedin are found in several tumor types and in normal muscle. The hormones seem to act mainly as contributing factors in the origin of tumors, but lack marked direct cancerigenic properties. However, the pursuit of hormones in blood and urine and tumor tissues, and their effects on the human body, has opened up a new and fruitful field in cancer service and research which is of great theoretic and practical interest. It now seems probable that a satisfactory classification of ovarian tumors may be based largely on their physiologic effects. The assay of Prolan is of value in the diagnosis and prognosis of testicular tumors. Many ingenious efforts have been made with some success to find among lower animals specific indicators of the presence of minute quantities of hormones, as thyroxin, estrin, intermedin and cortin. Many new clinical problems are arising in the analysis of tumors of the organs for specific hormones. Such investigations may not be regarded as interesting problems to be chosen at random, when a clinic has nothing else to do, but belong to the essential data required in the routine study and treatment of the cancer patient. To meet this demand a substantial staff of competent workers under the direction of an experienced physiologist or pathologist in an organized department of physiology is required.

Education—The conditions provided by a well systematized laboratory service in a cancer hospital are very favorable for the instruction of students and staff. There is a widespread feeling that in the university medical schools instruction in neoplastic diseases is not well organized and is inadequate for the importance of the subject. Cancer is the most curable of the major causes of death, and in this field the physician renders some of his most valuable services or makes his most regrettable mistakes. A

few lectures on the abstract theories of neoplasia, the microscopic study of a small series of sections of epithelioma, carcinoma and sarcoma, a review of the symptoms and treatment methods of cancer in the various clinical departments where conflicting views are apt to be expressed, leave the average student with the impression that malignant tumors are just another disease which he may safely undertake to diagnose and treat as he would pneumonia, appendicitis, or nephritis. With the concentration of material in a cancer hospital, it is possible to give in one month to small groups of students 180 hours of demonstration and instruction with intimate contact with many patients and covering the main branches of the whole subject. Aside from the limited information imparted, probably the main value of such a course lies in the point of view gained of the scope of the subject of cancer and the manner of approach to its problems. For the postgraduate student the opportunities for special instruction and experience in a cancer hospital outclass those possible in a general hospital. Whether or not one believes in high specialization in cancer service, there are few surgical services which may not benefit from the presence of some staff member who has passed through such a service in some American or European cancer hospital. Finally, the unusual facilities, equipment and materials found in the scientific laboratories of a cancer institute might well induce the postgraduate faculties of universities to extend their field of operations and grant degrees in course to students in physics, chemistry and biology, as illustrated in the cancer process. Some progress in this direction has already been made.

Comparing the complex organization now employed in the study and treatment of cancer with the conditions existing 40 or 50 years ago, it is difficult for those who have lived through both periods and witnessed the gradual changes to realize the revolutionary character of the progress made. Cancer can now be produced by a score of different methods, it can be cured by the skillful application of silent invisible radiant energy, its surgical treatment is now employed in a discriminating and highly skillful manner, the exciting causes of many of its major forms are well known. Biologists cultivate malignant cells in test tubes indefinitely, chemists have revealed some of the most intimate features of the metabolism of the cancer process, geneticists have demonstrated the subtle influence of hereditary factors, cancer research has employed the available knowledge of the fundamental sciences, an indifferent public has been aroused to a sense of its own responsibilities, and by combining all these agencies the outlook for the cancer patient has been greatly improved. These advances probably measure up to those witnessed in most other branches of human endeavor, and are probably quite as significant for human welfare as some of our more obtrusive achievements, as the combustion engine and the radio wave. There is no doubt that a necessary foundation has been laid for further progress, and possibly, as many believe, for new discoveries of great practical importance.

This brief review of the scope of organization of the modern cancer hospital and institute in this country and abroad should stand as assurance to the lay public, to workers in other sciences, to science editors, to directors of industrial research and to government officials, that the cancer problem probably is being handled about as well as may be in this generation with the facilities provided. If society is dissatisfied, then the first step should be to enlarge the resources of cancer service and research, and bring them more in line with those enjoyed by industrial research.

During the year 1936 the steel industries of America spent over \$10,000,000 in research. This is more than the total capital devoted to cancer research in this country. Or they may induce industrial research organizations to combine with the science departments of the universities and take over the so called problem of cancer which they interpret to be the secret of malignant growth, and let them put their own original views to practical test. There is plenty of cancer in every community. But no experienced oncologist will offer any promise that these or any other expedients available to present day science will immediately extend our knowledge of the ultimate nature of malignant overgrowth, or our control of disseminated cancer. On the contrary, history shows that the progress of the past 50 years has resulted mainly from the slow painstaking attack by pathologists and clinicians, on the problems as presented in the cancer patient, and experience indicates that future progress will be along the same tedious paths.

On the other hand, while a grand marshaling of forces designed to quickly reveal the so called secret of cancer may not be encouraged, an entirely different attitude may be taken toward an immediate and substantial increase of the resources available in cancer hospitals and institutes for the more comprehensive study of the host of solvable problems presented by the cancer patient. This is the type of cancer research that is comparable to industrial research, which has proven so productive of results, but the capital provided for cancer is absurdly small compared with that for industry. If the public will invest adequate capital in this type of cancer research directed to solvable practical problems, they can probably be assured of corresponding returns, but not under the present conditions.

REFERENCES

- ¹ Duplay Arch Gen, 601, 1875
- ² Poncet Gas d'hop, 41, 862, 1888
- ³ Collet Cent f Path, abstr, 1896
- ⁴ Volkmann Zeit f Chir, 41, 107, 1895
- ⁵ Kocher V A, 155, 532, 1899
- ⁶ Verse Arb a d path Instit Leipzig, 1908
- ⁷ Callender and Wilder Amer Jour of Cancer, 23, 25, 251, 1935

ABNORMAL FUNCTION OF THE COMMON BILE DUCT RESULTING FROM BENIGN CONDITIONS

WALTMAN WALTERS, M D , D Sc

ROCHESTER, MINN

DIVISION OF SURGERY, THE MAYO CLINIC

ABNORMAL function of the common bile duct is largely a matter of infection and obstruction, and, when the condition is benign, the two are intimately associated. Generally speaking, infection and obstruction of the common bile duct can be directly or indirectly related to inflammation which takes origin in the gallbladder.

Stones in the Common Duct—The most frequent cause of obstruction of the common duct is a biliary calculus which has been formed in the gallbladder and has been extruded from it into the common bile duct. Most such stones are faceted but occasionally a single ovoid stone, sometimes of the cholesterol type which is formed in the gallbladder, will be found to be the cause of obstruction of the common duct. Above such obstructing stones, not infrequently mushy, muddy, sandy material will be found in both common and hepatic ducts. This material is composed of cholesterol and bile pigment and is quite characteristic of the type of stones of the common duct which form secondarily.

That the clinical picture of biliary colic, followed by jaundice, is indicative of obstruction of the biliary tract, probably the result of a stone in the common duct, is well recognized. In 10 per cent of cases, however, in which the lesion is benign, the biliary obstruction is not the result of a stone in the common duct but is owing to inflammatory obstruction of the pancreas and extension of the inflammatory process into the liver, the process having its origin in the original inflammatory lesion of the gallbladder. On the other hand, a stone or stones may be present in the common bile duct without producing evidence of biliary obstruction, in such a case of diseased gallbladder it may be removed without exploration of the common bile duct and evidence of the presence of the calculi may appear later. The frequency with which stones are present in the common duct is emphasized by the fact that in the 812 operations performed at The Mayo Clinic, in 1936, for benign lesions of gallbladder and common duct, stones were found in the common duct or hepatic duct in 109. Repeated attacks of colic direct attention to the common bile duct but not infrequently, because of the absence of a history of jaundice or of chills and fever, the probability is not taken into consideration that a stone in the common bile duct can be overlooked. I believe that the possibility of stones in the common bile duct being overlooked could be reduced to an absolute minimum if a portion of the common duct was always exposed as part of the operation of cholecystectomy. Not only would this give an accurate view

of a portion of the duct, so that the surgeon could determine its size and whether or not there was infection in its wall, but in addition it would prevent the possibility of injuring the duct during the performance of cholecystectomy

One surgeon⁸ said that he opened the common duct for exploration only when he could feel stones. In my experience, adhering to this plan would have meant that small stones in the hepatic ducts or in the ampulla would have been overlooked in approximately 30 to 50 per cent of the cases upon which I have operated. Enlargement of the common duct, associated with any evidence of obstruction, is almost an infallible indication that obstruction is actually present. The obstructing agent will not always be a stone, but when the duct is enlarged it always should be opened and the interior of it, as well as that of the hepatic duct, should be diligently searched for stones. It has been the custom at The Mayo Clinic for 35 years, when the

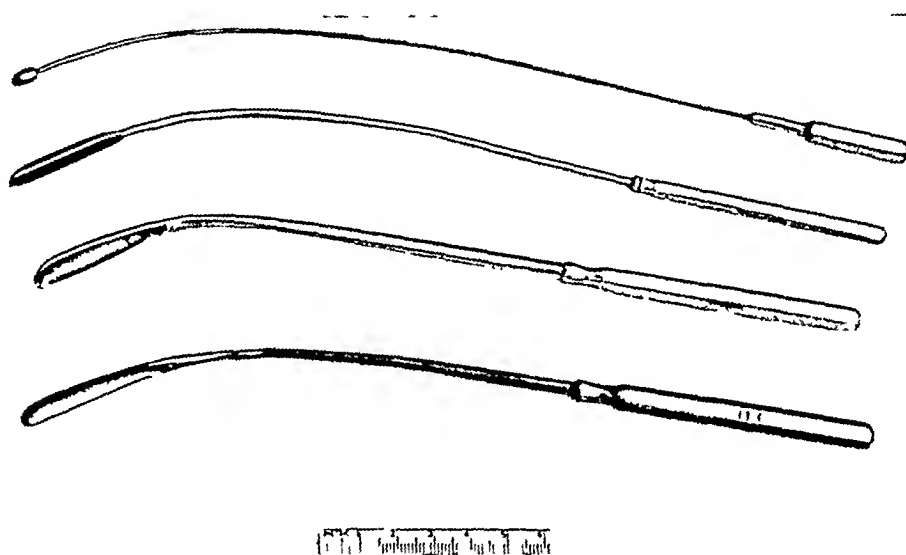


FIG 1—Scoops for exploring common and hepatic ducts for stones and dilating the sphincter

duct has been opened for exploration, to pass exploring scoops through the lower end of the duct into the duodenum to dilate the sphincter. A scoop 4 or 5 Mm in diameter is first used and larger scoops are then passed until one 8 Mm in diameter has been used. The scoops which are represented in Fig 1 have the distinct advantage not only of serving as sound-like dilators of the sphincter, but in addition they allow any small stones to be engaged in the hollow of the scoop, thus permitting their removal. Dilatation of the sphincter accomplishes two purposes. First, it allows passage through it of hepatic duct stones which might have escaped the exploring scoop, second, by dilatation, the development of postoperative spasm of the sphincter probably is reduced considerably. That spasm of the sphincter of Oddi is a definite factor in the causation of biliary colic cannot be denied, and a more detailed discussion of this will be considered later.

Choledochography or Cholangiography and the Forced Passage of Re-

tained Common Duct Stones—The use of choledochography or cholangiography, namely, roentgenographic examination of the outline of the common bile duct after injection of a substance that is opaque to roentgen rays (biominol, lipoiodine) both at the time of operation and subsequent to it, as has been suggested by Overholt, Mirizzi, by Thiessen and me, and by Best and Hicken, and Hicken, Best and Hunt, has given valuable information not only regarding the size of the common bile duct but also regarding its emptying time and the presence of persisting obstruction

In a case in which I recently operated, the patient was obese and had undergone an operation on the biliary tract elsewhere. I removed a large stone from the ampulla. At that time it was impossible to explore the intrahepatic duct because a large, anomalously placed hepatic duct covered most of the common duct. Although dilation of the sphincter of Oddi was carried out by means of exploring scoops, two weeks subsequent to operation, when the T tube was closed, attacks of biliary colic again occurred. A choledochogram revealed a circumscribed filling defect apparently caused by a stone, in the lower end of the common bile duct (Fig 2A). Repeatedly, closure of the T tube was followed by attacks of biliary colic. Using the method of instillation of ether into the common bile duct as suggested by Pribram, and diluting the ether with alcohol as suggested by Osterberg, the stone was fragmented (Fig 2B). Then, by closing the T tube after the mixture of alcohol and ether had been introduced, sufficient pressure was produced within the common bile duct so that the fragments of stone were forced through a relaxed sphincter of Oddi, this relaxation had been accomplished by having the patient inhale an ampule of amyl nitrite. A choledochogram then disclosed that the gallbladder was free of defects and that its contents were emptying normally into the duodenum (Fig 2C).

This method of clearing the common bile duct of stones is worthy of emphasis. It places distinct importance on the use of choledochography as a method of interpreting the physiologic function of the common bile duct subsequent to operations on it.

Spasm or Inflammation of the Sphincter of Oddi—A great deal of excellent work has been done on the anatomy of the sphincter of Oddi. In a recent review of the subject, Boyden has given a detailed account of the contributions in this field. He attributed to Vesalius the first description of the sphincteric mechanism at the lower end of the common bile duct, and he credited Oddi, Hendrickson, Nuboer and Westphal with descriptions relative to the anatomy and physiology of the structure.

McGowan and Butsch,^{3, 6} Fellows in Surgery in The Mayo Foundation, studied, with me, a group of patients who had been operated upon because of biliary colic. The common bile duct of each patient had been opened and explored, in some cases stones had been found and in some cases they had not. A T tube had been inserted in each case. In some cases attacks of colic continued after operation. The presence of the T tube allowed McGowan and Butsch to determine in these cases whether the

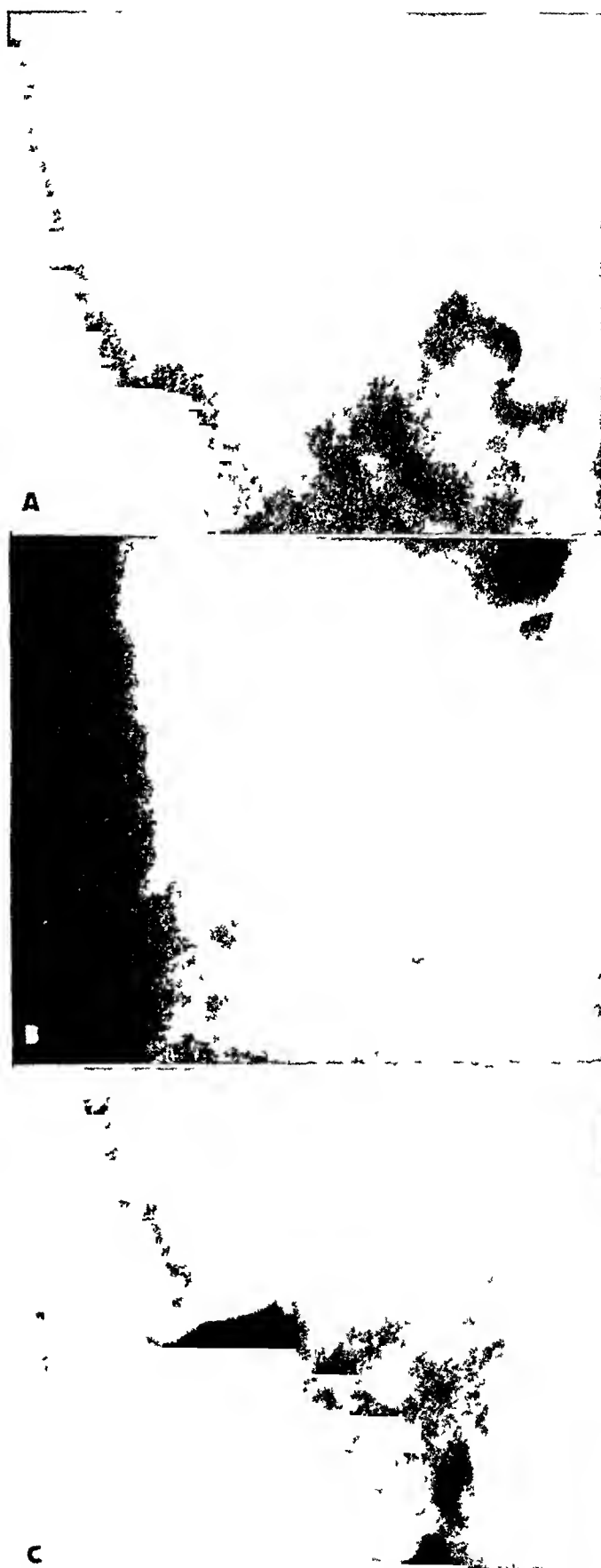


FIG 2—(A) Cholangiogram showing filling defect in the lower end of the common bile duct (B) Cholangiogram showing apparent fragmentation of the stone in the lower end of the common bile duct (C) Cholangiogram showing common bile duct free of defects and emptying normally

intraductal pressures remained within the normal range of 0 to 30 Mm of water or whether they had increased. The investigators could be reasonably sure that stones were no longer present, but they found, simultaneous with attacks of colic, pressures within the common bile duct of as much as 110 or even 160 Mm of water (Chart 1, above). Administration of morphine, 1/6 gr (0.01 Gm), aggravated the pain and increased the intraductal pressure. The same was true, but to a less marked degree, when codeine, dilaudid or pantopon was administered. Inhalation of amyl nitrite and the placing of 1/100 gr (0.0006 Gm) of nitroglycerin under the tongue relieved the pain and reduced the pressure within the common bile duct, it was assumed, therefore, that these two drugs, amyl nitrite and

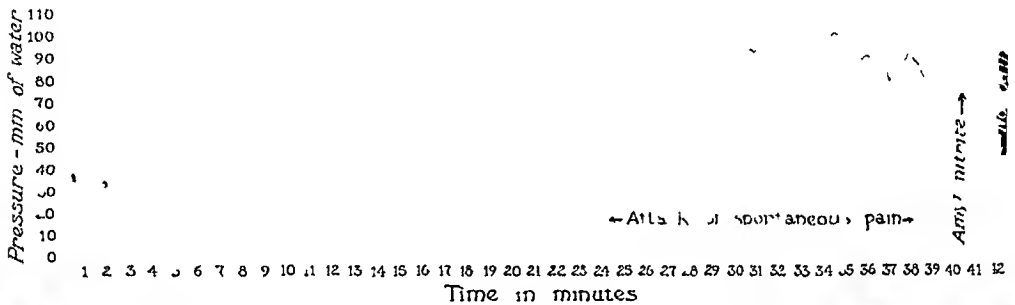


CHART 1—(Above) Showing increase in intraductal pressure during an attack of pain. (Below) Precipitation of biliary colic with increase in intraductal pressure by the administration of morphine

nitroglycerin, had relaxed the sphincteric mechanism at the lower end of the common bile duct. These observers also found that in some cases in which stones had not been found in the common bile duct, an attack of biliary colic, with increased intraductal pressure, could be precipitated by administration of morphine (Chart 1, below), codeine, pantopon or dilaudid, and after the precipitation of such attacks their relief, as well as a decrease in intraductal pressure, likewise could be obtained by using the antispasmodic substances, amyl nitrite and nitroglycerin. When a substance opaque to roentgen rays (lipiodine) was injected into the bile ducts and roentgenograms were made, it was noted that, with the attack of pain, spasm at the lower end of the common bile duct occurred and the opaque substance filled the intrahepatic ducts. With the administration of amyl nitrite or nitroglycerin, the spasm of the lower end of the duct ceased, the intrahepatic

and common bile ducts emptied of the opaque substance, intraductal pressure decreased, and the patient was relieved of pain

This work is of outstanding importance, too, because, among other things, it emphasizes the fact that abnormal function of the sphincteric mechanism of the lower end of the common bile duct is intimately associated with pain which occurs with some lesions of the biliary tract. It should not be assumed in any case that spasm of the sphincter of Oddi alone is the cause of postoperative biliary colic, for in several cases studied stones have been removed from the common bile duct and in others pancreatitis has been demonstrated at subsequent operation. There is no question in my mind but that most patients who continue to have biliary colic subsequent to operation usually have either a stone or stones in the common or hepatic ducts, or pancreatitis, as factors in production of the pain. It should not be assumed that spasm of the sphincter exists independently until the common duct has been opened and thoroughly explored for stones. However, if the usual precipitating factors are absent, and if it is proved by postoperative studies of intraductal pressure and by roentgenographic studies, that intraductal pressure is abnormally high, that the ducts do not empty and that opaque substances fill the ducts in a retrograde direction, then local abnormality of the sphincter of Oddi should be considered.

Infection—The problem of infection associated with abnormal function of the common bile duct deserves emphasis and elaboration. That acute inflammation of the gallbladder can produce mild jaundice without there being a stone in the common bile duct is well recognized. This jaundice is largely the result of extension of the inflammation, not only through the lymphatic channels but also through the walls of the biliary tract, into the liver and into the pancreas. With edema of the pancreas, sufficient obstruction of the common bile duct occurs to bring about stasis in the common bile duct and, with this stasis, and with the infection present in the gallbladder, the contents of the common bile duct become infected. In cases of acute, subacute and chronic inflammation of the biliary passages, in which the common bile duct was opened for exploration, the presence of gram-negative bacilli, sometimes associated with Streptococci and Staphylococci, has been a frequent finding in my experience. Relief of the biliary obstruction in these cases has been followed by subsidence of infection and disappearance or alleviation of the evidence of disease of the biliary tract. The obstruction has been relieved either by cholecystostomy and removal of the obstructing stone in the cystic duct, or better still, by cholecystectomy if acute or subacute infection of the gallbladder is present, relief also has been effected by removal of stones from the common bile duct or, if stones were not present, by drainage of the common bile duct. In these cases, likewise, choledochographic study of the contour of the duct and of its emptying time, subsequent to operation, has been of the greatest value.

On several occasions, when clinical trial at closure of the T tube indicated that the common bile duct was emptying normally, it has been found

on choledochography that the duct remained enlarged and maintained its tendency to retain infected bile. I think it has been in this group that, prior to routine choledochography, symptoms have recurred because of too early removal of the T tube. For the last two and one-half years I have held to the belief that the T tube should not be removed from a dilated, partially obstructed common bile duct until its contour has returned to normal and until it empties in a normal fashion, that is, in ten minutes. In one case dilatation of the duct persisted for more than three months (Fig 3A). In this case closure of the T tube, too, was followed by pain. The T tube was allowed to remain in place for an additional three months, when choledochography disclosed that the common bile duct was of normal size and was emptying normally (Fig 3B). Then closure of the T tube was

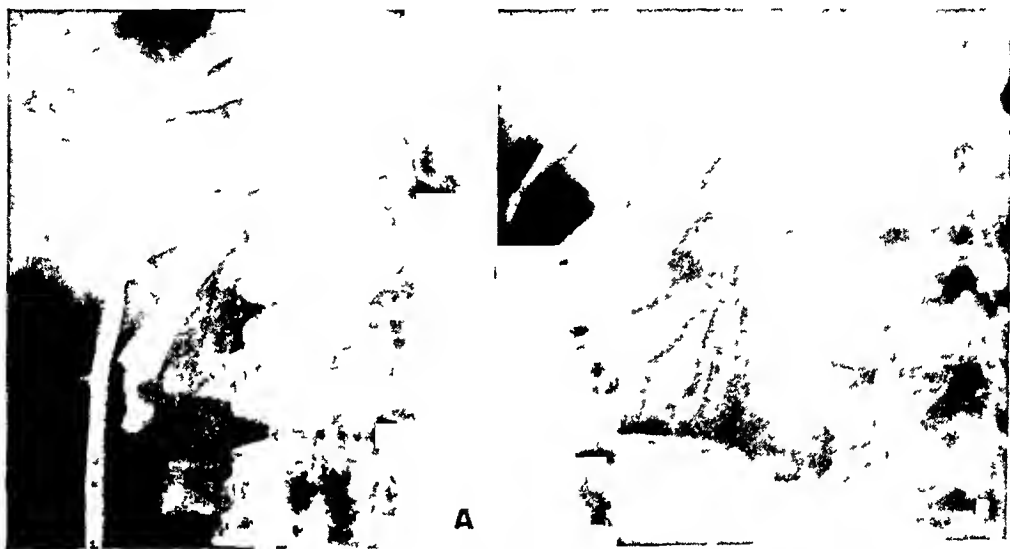


FIG 3—(A) Choledochogram showing persisting dilatation of the common bile duct three months after transduodenal removal of common duct stone. (B) Choledochogram showing that same duct is normal in size at end of six months of drainage.

not followed by pain. Subsequent to removal of the T tube, the patient has been well. In several cases in which biliary colic appeared subsequent to cholecystectomy, the common bile duct was found to be enlarged, and when it was opened and explored it was found not to contain stones, but thickening of the head of the pancreas was demonstrable by palpation. The persisting narrowing of, and stasis in, the common bile duct had been demonstrable for several weeks subsequent to operation (Fig 4A and B), and in a few of these cases reflux of the injected substances into the pancreatic duct was demonstrable (Fig 5). What part this reflux played in the persistent pancreatitis is, of course, difficult to determine.

Stricture of the Common Bile Duct—Only the briefest reference can be made at this time to some of the important pathologic and physiologic changes demonstrable in cases in which obstruction and infection are associated with stricture of the common bile duct.

Evidence has been presented which would indicate that an obliterative

ABNORMAL FUNCTION OF COMMON DUCT

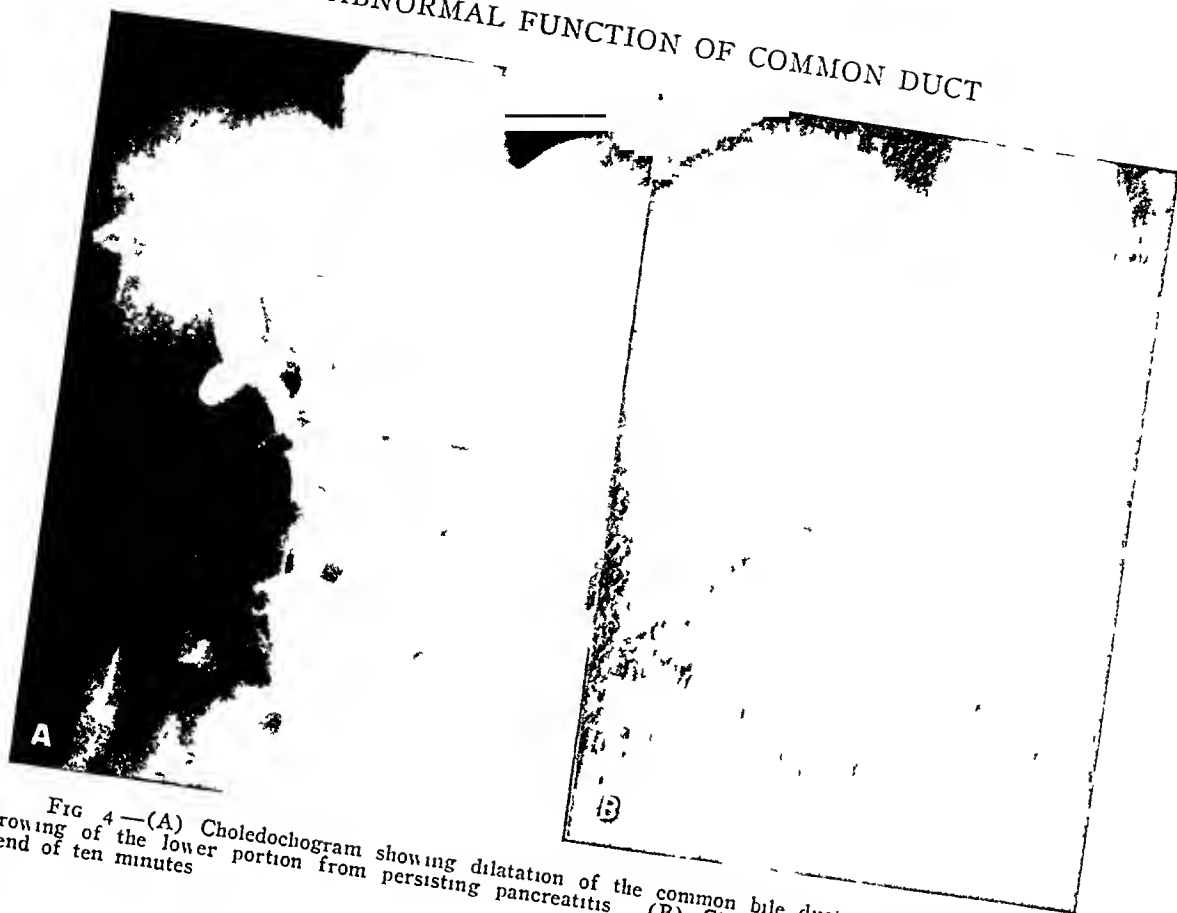


FIG 4—(A) Cholangiogram showing dilatation of the common bile duct with stasis and narrowing of the lower portion from persisting pancreatitis (B) Cholangiogram shows retention at end of ten minutes



FIG 5—Cholangiogram showing dilatation of ducts with reflux of opaque media up pancreatic duct Patient had been operated upon for biliary colic Pancreatitis was found there was no stone in the common duct

infection which occurs spontaneously may produce stricture of the common bile duct. Fortunately such cases are rare. Most strictures of the common bile duct are traumatic and more or less localized, and fortunately there is usually sufficient normal duct above the stricture that anastomosis can be made between it (above the stricture) and an opening made in the duodenum. In such cases the results of the operation are dependent on three factors. First of all, that infection in the wall of the duct above the stricture, and within the liver, is not so severe that it cannot subside when the obstruction has been relieved by the anastomosis, second, that sufficient duct be present to allow accurate anastomosis between it and an opening made in the duodenum, and third, that so much damage has not taken place to the hepatic parenchyma, as a result of obstruction and infection from the stricture, that it cannot return to reasonably normal function after relief of the biliary obstruction. The capacity of the liver to return to reasonably normal function when an accurate anastomosis can be carried out is astounding. I think the points that are well worth emphasizing, therefore, are that if there is sufficient normal duct above the stricture that accurate anastomosis can be made between it and an opening in the duodenum, and if the liver is in good condition and is without too much infection, the chances of a persisting excellent result from the operation are very good. Forty-eight per cent of a group of 29 patients who had stricture of the common bile duct, upon whom I had operated, between 1924 and 1933, were living and in good condition when studied in 1936. When the additional 22 patients operated upon, between 1933 and 1936, were included, making a total of 51 cases, approximately 57 per cent of the entire group were living and well^{10, 14}. Experience has shown that choledochoduodenostomy or hepaticoduodenostomy has been the preferable procedure for stricture of the bile ducts, and the best results have been obtained in those cases in which operation was performed early in the course of the biliary obstruction and in which the liver had been injured very little by either cirrhosis or infection.

SUMMARY

Abnormal function of the common bile duct is largely a matter of infection and obstruction associated with biliary calculi and other benign obstructive lesions of the biliary tract, such as pancreatitis and cholangitis, stricture of the common bile duct and abnormal function of the sphincter of Oddi.

The high incidence of stone of the common duct associated with cholelithiasis leads one to assume that, in many cases, stones of the common duct are being overlooked. This possibility could be reduced to a minimum if all dilated common bile ducts were opened and explored for stones even though stones could not be palpated through the walls of the ducts.

Introduction of a T tube into the common bile duct for drainage following exploration has allowed study of the size and rapidity of emptying

of the common bile duct (choledochography, cholangiography) Such roentgenologic studies reveal the presence of persisting obstruction and indicate their cause, such as inflammatory thickening in the head of the pancreas, abnormal function of the sphincter of Oddi and overlooked stone in the common duct In a recent case, in which a stone persisted in the common duct, fragmentation of the stone and forcible expulsion of it into the duodenum occurred after introduction of ether and alcohol into the common duct after the sphincter of Oddi had been caused to relax by administration of amyl nitrite

Studies indicated that pressure of as much as 160 Mm of water occurred within the common bile duct during an attack of biliary colic In some cases such an attack can be precipitated by administration of morphine 1/6 gr (0.01 Gm) During the attacks of pain the use of an antispasmodic substance, nitroglycerin or amyl nitrite, has relaxed the sphincteric mechanism at the lower end of the common bile duct, reduced the intraductal pressure and relieved pain

Abnormal function of the sphincter of Oddi usually occurs secondarily to retention of stones in the common bile duct and pancreatitis but in a few cases it may occur independently Acute and subacute inflammatory changes in the gallbladder progress through the walls of the common bile duct and through the lymphatic channels into the pancreas and liver, producing jaundice without stones of the common duct in approximately 10 per cent of cases Removal of the infected gallbladder and drainage of the common bile duct not only have removed the source of infection in the gallbladder but infections in the pancreas and liver have subsided secondarily

Cholodochography, in these cases, has been of the greatest assistance in determining the propitious time to remove the T tube from the common bile duct On several occasions in which it was thought that drainage had been of sufficient duration, choledochograms gave evidence of persisting enlargement of the common bile duct, with delay in its emptying Reflux of the opaque substance into the pancreatic duct has been demonstrated

REFERENCES

- ¹ Best, R. R., and Hicken, N. F. Biliary Dyssynergia, *Physiological Obstruction of the Common Bile Duct* Surg, Gynec & Obstet, 61, 721-734, December, 1935
- ² Boyden, E. A. The Pars Intestinalis of the Common Bile Duct, as Viewed by the Older Anatomists (Vesalius, Glisson, Bianchi, Vater, Haller, Santorini, etc) Anat Rec, 66, 217-232, September, 1936
- ³ Butsch, W. L., McGowan, J. M., and Walters, Waltman. Clinical Studies on the Influence of Certain Drugs in Relation to Biliary Pain and to the Variations in Intrahepatic Pressure Surg, Gynec & Obstet, 63, 451-456, October, 1936
- ⁴ Hendrickson, W. F. A Study of the Musculature of the Entire Extra-hepatic Biliary System, Including that of the Duodenal Portion of the Common Bile-duct and of the Sphincter Bull Johns Hopkins Hosp, 9, 221-232, September-October, 1898
- ⁵ Hicken, N. F., Best, R. R., and Hunt, H. B. Cholangiography, Visualization of the

Gallbladder and Bile Ducts During and After Operation ANNALS OF SURGERY,
103, 210-229, February, 1936

⁶ McGowan, J M, Butsch, W L, and Walters, Waltman Pressure in the Common
Bile Duct of Man, Its Relation to Pain Following Cholecystectomy J A M A, 106,
2227-2230, June 27, 1936

⁷ Mirizzi, P L La cholecystectomie sans drainage (cholecystectomie ideale) Paris,
Masson et Cie, pp 105, 1933

⁸ Moynihan, Berkeley Abdominal Operations Ed 4, Philadelphia, W B Saunders Co,
2, pp 642, 1926

⁹ Nuboer, J F Studien uber das extrahepatische Gallenwegssystem Frankfurter
Ztschr f Path, 41, 198-249, 1931

¹⁰ Nygaard, K K, Shelden, C H, and Walters, Waltman Strictures of the Bile Ducts,
Results in Fifty-one Operative Cases Proc Staff Meet Mayo Clinic, 12, 25-29,
January 13, 1937

¹¹ Oddi, Ruggero Quoted by Boyden, E A

¹² Overholt, R H Biliary Tract Visualization with Radiopaque Oils Surg, Gynec &
Obstet, 52, 92-97, January, 1931

¹³ Pribram, B O New Methods in Gall-stone Surgery Surg, Gynec & Obstet, 60,
55-64, January, 1935

¹⁴ Walters, Waltman Discussion Proc Staff Meet Mayo Clinic, 12, 29-30, January 13,
1937

¹⁵ Walters, Waltman, and Thiessen, N W Visual Methods of Studying the Physiology
of the Common Bile Duct I The Problem of Pancreatitis and Sphincteritis Proc
Staff Meet Mayo Clinic, 9, 772-775, December 19, 1934

¹⁶ Westphal, K Quoted by Boyden, E A

CONGENITAL ATRESIA OF THE BILE DUCTS

EDWARD J DONOVAN, M D

NEW YORK, N Y

CONGENITAL atresia of the bile ducts is a rare condition, but we have had 16 cases at the Babies Hospital during the past ten years. Although this is a small group when compared with 21,000 admissions during the same period, these cases have occurred frequently enough to justify reporting them. I have two other cases which were operated upon at St. Luke's Hospital to add to this group.

The exact etiology of this condition is unknown, and while many theories have been advanced to explain its cause, the most plausible one apparently is that the obliteration of the bile ducts is due to a failure of the ducts to canalize during development, and the accompanying cirrhosis of the liver is secondary, resulting from the obstruction to the outflow of bile. This theory easily explains the findings in many cases.

The embryologic development of the liver and bile duct system is so complex that one wonders why more developmental errors do not occur. The liver, which is the first gland of the digestive tract to appear, is first seen in embryos of 3 Mm as a longitudinal evagination from the entoderm of the ventral surface of the gut in the duodenal area. The cephalic portion of the evagination is solid. It is destined to become the liver proper, and is called the *pars hepatica*. The caudal portion of the original evagination, called the *pars cystica*, is hollow, its cavity being continuous with the lumen of the gut, and is the part from which the gallbladder and extrahepatic ducts are to arise. Beginning at both ends, the evagination constricts itself from the gut so that in an 8 Mm embryo, its only connection with the intestine is a narrow cord of cells, the anlage of the common duct.

The *pars hepatica* grows very rapidly and remains attached to the common duct by a short cord of cells which will later become the hepatic duct. The *pars cystica*, which also increases in size rather rapidly, is connected with the common duct by a short cord of cells, later to become the cystic duct. The *pars cystica* grows into the ventral mesentery and thus becomes surrounded by mesodermal tissue, its proximal portion continues to elongate and form the cystic duct, the distal portion becomes larger and more dilated and forms the gallbladder. The *pars hepatica* also grows into the ventral mesentery and becomes surrounded by mesodermal tissue which gives rise to the capsule of Glisson. Most authors believe that the extrahepatic ducts during development lose their lumens through epithelial proliferation to become solid cords, later becoming recanalized.

The pathologic changes presented in these cases are quite variable, depending to a large extent upon the age of the patient, since the process is

rapidly progressive. Any portion of the bile duct system may be wanting. The gallbladder may be present, often small and colorless, or it may be completely absent, as it was in two of our cases. The obliteration of the ducts may be found anywhere, but it is often in the region of the common duct. The liver is usually dark green in color, very much enlarged, hard and irregular. On microscopic section, there is, in various degrees, replacement of normal liver structures by fibrous tissue.

The clinical picture in congenital atresia of the bile ducts runs quite true to form. Jaundice may be present at birth, but more often the baby appears quite normal, becoming jaundiced two or three days later. At first, the stools, while they may be colored, give a negative test for bile, but they soon become clay colored or white. The jaundice increases rapidly so that at the age of three or four months, these patients have a grayish-green color. Bile is present in the urine in large quantities, and, if the atresia is complete, the liver increases rapidly in size and soon becomes nodular. In most cases, the spleen is also enlarged. The blood shows an increased bile index and a positive immediate direct van den Bergh reaction. The clinical picture is usually one of progressive decline, with increasing jaundice, constantly enlarging liver and spleen, followed by death at about the age of six months. A few cases have been reported where these children with complete atresia have lived to be 15 months of age.

The prognosis for complete atresia is invariably fatal. One of the patients of this series was 14 months old at death. When the obliteration is incomplete, surgery offers great hope. Unfortunately, the obliteration was so complete in most of our cases that nothing could be done for them, and in most instances, autopsy confirmed the operative findings. Ladd¹² has been more fortunate in his series, having found eight of 11 cases amenable to surgery. Only one of our 18 cases was helped by surgery. Two cases thought to be hopeless at operation are alive and well two and one-half and three years after operation. I am completely at a loss to know how to explain these two cases. Both patients had all of the requisites for such a diagnosis. At operation the ducts were well exposed and examined carefully. They appeared only as fibrous cords and had every indication of being undeveloped. Obviously we were mistaken in our diagnosis, as neither child has had symptoms of atresia since the jaundice disappeared after operation.

In making the diagnosis of congenital atresia of the bile ducts, it is necessary to eliminate (1) Icterus neonatorum, which usually disappears before the patient is two weeks old, (2) syphilitic hepatitis, which may be excluded by serology of the patient and his parents in the absence of other stigmata of syphilis, (3) congenital hemolytic icterus, which is rarely found in such young children, may be excluded by a normal fragility of the red cells, (4) jaundice of sepsis, which may be ruled out by the absence of fever, and by negative blood culture and the absence of other signs of sepsis, (5) jaundice due to pressure on the common or hepatic ducts by

enlarged lymph nodes We have had one case who had a typical history of atresia of the bile ducts who was successfully operated upon for obstruction of the common duct Autopsy four months later showed the common duct obstruction to be due to tuberculosis of the hepatic lymph nodes

The aim of surgery in these cases is to deliver the bile into the intestinal tract, and any operation which may accomplish this is worth while Cholecystgastrostomy and cholecystoduodenostomy are excellent procedures if there is enough of the duct system present to effect such an anastomosis If not, drainage to the outside may be established, creating an external biliary fistula which may later be implanted into the stomach or duodenum Saline should be injected into the ducts at operation in the hope that the obstruction may be due to a mucous plug which may be forced out Obviously all of these cases deserve an exploratory celiotomy, hoping that there is enough of the duct system present to do some of the above procedures

ABBREVIATED REPORTS OF 18 CASES

Case 1—M R, a female, age three months, was admitted to St Luke's Hospital with a history of increasing jaundice, clay colored stools and dark colored urine since the age of two weeks She had vomited many times since birth but there had never been any bile in the vomitus Plaster encasement of both feet for talipes varus The family history was negative Well developed, well nourished but deeply jaundiced Liver was palpable 4 cm below the costal margin and the spleen was palpable Blood count normal, urine was bile positive, stools bile negative Bile index 83, blood calcium 11.4, blood phosphorus 7 Van den Bergh immediate direct positive At operation the liver was enlarged, dark green in color but smooth The gallbladder was very large and filled with bile The cystic duct was distended and entered the common hepatic duct directly The common duct was absent Cholecystgastrostomy was effected by suture just proximal to the pylorus Convalescence was uneventful and the first stool (48 hours after operation) was positive for bile The bile index one week after operation had dropped to 20, and the jaundice disappeared rapidly This patient has been followed for four and one-half years and is normal in every way Another child born to these parents two years ago showed no abnormalities

Case 2—J G, a white female, age three weeks, was admitted to St Luke's Hospital with a history of rapidly increasing jaundice, dark colored urine and clay colored stools since the first day after birth Two children of this family had died of jaundice at the ages of three months and three weeks respectively The family history was negative otherwise Bile index was 50, van den Bergh immediate, direct was positive, urine was bile positive, stools bile negative, fragility of the red cells was normal, Wassermann on patient and parents negative The patient was observed for 16 days and seemed to be getting worse rapidly She was transfused three times At operation the liver was large, dark green and smooth The gallbladder was small and colorless, the common and hepatic ducts looked like fibrous cords The abdomen was closed because the condition did not seem to be amenable to surgery The convalescence was uneventful and she was discharged from the hospital two weeks later, all stools in the convalescent period were bile negative and the jaundice was not better Shortly after being discharged from the hospital she began to gain in weight, the jaundice gradually disappeared and the stools at the same time became colored She has been followed for three years and has remained entirely free from symptoms This patient had everything necessary to make a diagnosis of congenital atresia of the bile ducts and at operation our suspicions seemed to be confirmed The obstruction in this case must have been due to a mucous plug or a temporary failure of the ducts to open in the region of the portal fissure It is possible that this was

a case of icterus gravis which recovered, since there is a family history of two deaths in children, both of whom were jaundiced

Case 3—H C, a white male child, was admitted to the Babies Hospital with a history of increasing jaundice, dark colored urine and clay colored stools since birth. Poorly nourished, deeply jaundiced infant of two months of age, urine bile positive, stools bile negative, van den Bergh immediate, direct positive. Operation showed a small gallbladder which was colorless and empty. The extrahepatic ducts seemed to be completely undeveloped. The liver was large, dark green in color and smooth. The patient died 16 days after operation. No autopsy.

Case 4—E R, a white female child, age two months, was admitted to The Babies Hospital with a history of increasing jaundice since birth. Liver and spleen were easily palpable, R B C 3,000,000, Hb 75 per cent, coagulation and bleeding time normal, icterus index 93.7, van den Bergh immediate, direct positive. Urine positive for bile, stools bile negative. Operation revealed completely undeveloped gallbladder and extrahepatic ducts with the liver large, firm and dark green in color. Died eight days after operation. No autopsy.

Case 5—C A, a white male, age four weeks, with a history of jaundice, dark colored urine and clay colored stools since birth. Well nourished, well developed and deeply jaundiced. Liver and spleen easily palpable, prominent superficial veins on the abdomen. Urine was bile positive, stools bile negative, icterus index 82.5, van den Bergh immediate, direct positive. Developed bronchopneumonia three days after admission and the blood culture was positive for hemolytic *Streptococcus*. One week later the patient was taken home against advice. We have been unable to obtain further information about him. This patient had everything necessary to make a diagnosis of congenital atresia of the bile ducts, but in addition had *Streptococcus* sepsis with bronchopneumonia. It is possible that this was a case of jaundice due to sepsis, but I doubt it as the sepsis seemed to be a terminal affair.

Case 6—L P, a white male, age four months, was admitted to The Babies Hospital, having had jaundice since birth. The urine had always been dark and the stools always light in color. The liver and spleen were easily palpable. Van den Bergh immediate, direct positive, urine bile positive, stools bile *positive*, icterus index 41.6, Kahn negative. This case was thought to have a partial atresia of the bile ducts and to offer a good chance of being helped by surgery. He developed a high fever, had blood and mucus in the stools and was taken home against advice, without operation.

Case 7—E E, a white female, age two months, was admitted to the Babies Hospital with a history of jaundice since birth. Liver and spleen were enlarged, urine bile positive, stools bile negative, icterus index 155, van den Bergh immediate, direct positive. Operation disclosed a gallbladder which was very small and colorless with the extrahepatic ducts appearing as fibrous cords. The liver was quite large, dark green in color with an irregular surface. This condition was not amenable to surgery. The postoperative course was one of progressive decline, increasing jaundice, loss of weight, emaciation, and death 37 days later. The autopsy showed the liver to be dark green in color and very firm with an irregular surface. On section it gritted under the knife and showed an increase in connective tissue about the portal spaces. The gallbladder measured only 2 cm in length and contained only 0.5 cc of thin colorless fluid. Leading from the gallbladder was a narrow duct which could be traced for only 2.5 cm, and ended blindly without communication with the intestine or other duct. The hepatic ducts were completely obliterated and the common duct was not present (Fig 1).

Case 8—M C. Second admission of a white female, age five months, deeply jaundiced since birth. Admitted three months previously, at which time the bile index was 150, van den Bergh immediate, direct was positive, urine was bile positive, stools were bile negative. Taken home against advice. She is now deeply jaundiced, poorly nourished, and has a large liver and a large spleen. At operation the gallbladder was small and colorless, the extrahepatic ducts were completely undeveloped. There was

ATRESIA OF BILE DUCTS

nothing that could be done toward correcting the condition. She developed a respiratory infection after operation and coughed a great deal. The abdominal incision broke open six days after operation and had to be resutured under anesthesia. The patient died 15 hours later. No autopsy.

Case 9—F L, a white male, age seven weeks, admitted to the Babies Hospital with a history of jaundice since the fourth day of life. The jaundice had increased rapidly, the urine had always been dark colored and the stools clay colored. Poorly developed premature infant with a very large liver and a large spleen. He also had an undescended left testicle and an hypospadias. The urine was positive for bile, the stools were bile negative, van den Bergh immediate, direct was positive. In spite of transfusions, infusions, *etc*, the course was progressively down hill and he died 13 days after admission. This child's condition never was such that operation could be considered. No autopsy.



FIG 1.—Photograph of liver showing rudimentary gallbladder, cystic duct ending blindly, common duct absent.

Case 10—H F, a white male, age eight weeks, was admitted to the Babies Hospital with a history of jaundice, clay colored stools and dark urine since birth. He had the characteristic findings of Mongolian idiocy. Blood count, Kahn and tuberculin were negative. Urine positive for bile, stools were bile negative, fragility of the red cells was normal, van den Bergh immediate, direct was positive. He also had a congenital malformation of the heart. He was taken home against advice.

Case 11—J C, a white female, age six weeks, was admitted to the Babies Hospital with a history of jaundice, clay colored stools and dark urine since the age of one week. Deeply jaundiced, poorly nourished, with a large liver and a palpable spleen. Urine bile positive, stools negative for bile, Kahn and tuberculin negative, van den Bergh immediate, direct positive. At operation the gallbladder was absent and the bile ducts completely undeveloped. She died at home six months later.

Case 12—G D, a white female, age seven months, was admitted to the Babies

Hospital with a history of jaundice, clay colored stools and dark colored urine since birth. Deeply jaundiced with a large liver and a large spleen. Van den Bergh immediate, direct positive, urine positive for bile, stools bile negative. Four days after admission she developed acute otitis media followed by a fulminating pneumonia and death two days later. Blood culture positive for hemolytic *Staphylococcus albus*. This case had all of the requirements to make a diagnosis of congenital atresia of the bile ducts, but died of a terminal sepsis without operation. No autopsy.

Case 13—H C, a white female, age four and one-half months, was admitted to the Babies Hospital with a history of jaundice, clay colored stools and dark colored urine since the age of three days. Deeply jaundiced, with a large liver and a large spleen and signs of fluid in the peritoneal cavity. Blood count, fragility of the red cells, Kahn and tuberculin were negative. While being prepared for operation she developed otitis media, the abdomen became distended and a peritoneal puncture revealed *Streptococcus hemolyticus*. Blood culture positive for *Streptococcus hemolyticus*. Patient died eight days after admission. Autopsy showed complete obliteration of the cystic, common and hepatic ducts, undeveloped gallbladder, biliary cirrhosis of the liver, splenomegaly, congenital malformation of the heart and fibrinopurulent peritonitis.

Case 14—L G, a white male child, age 27 days, with a history of jaundice, clay colored stools and dark colored urine since birth. Abdomen had always been large. Was circumcised at the age of eight days and bled for three days. He was deeply jaundiced, with a large liver and a large spleen. Blood count, Kahn, tuberculin, fragility of the red cells were normal, van den Bergh immediate, direct was positive, gastric lavage on five different days revealed no bile. Urine positive for bile, stools bile negative. Operation showed about 150 cc of bile stained fluid in the peritoneal cavity. The liver was enormous, hard and dark green in color, the gallbladder and bile ducts were undeveloped. The condition was not amenable to surgery. The postoperative course was progressively down hill and the patient died three weeks after operation. Autopsy revealed an undeveloped gallbladder with an anomalous insertion of the cystic duct into the right hepatic duct. There was complete obliteration of the common duct, biliary cirrhosis of the liver, splenomegaly, patent foramen ovale and ductus arteriosus.

Case 15—A D, a white male, age two months, was admitted to the Babies Hospital with a history of jaundice, clay colored stools and dark urine since birth. Emaciated, deeply jaundiced child with a large liver and a large spleen. Blood count, Kahn and tuberculin negative. Stools were negative for bile, urine positive, van den Bergh immediate, direct positive. He developed acute otitis media and an upper respiratory infection and was operated upon when these infections had completely subsided. The liver was very large and cirrhotic, the gallbladder was absent and the extrahepatic ducts completely undeveloped. The postoperative course in the hospital was uneventful and he died at home one month after discharge.

Case 16—K L, a Negro male, age three months, was admitted to the Babies Hospital with a history of jaundice since birth. Mother had been treated for lues when she was four months pregnant. Three other children alive and well. Blood count, Kahn, tuberculin negative. Urine bile positive, stools bile negative, van den Bergh immediate, direct positive. Gastro-intestinal roentgenologic examination showed the stomach to be on the right side. At operation the liver was large, dark green in color and situated on the left side. The stomach was on the right side, the colon completely on the left side, the gallbladder was small and colorless and the extrahepatic ducts completely undeveloped. He was discharged home one month after admission and readmitted two months later with pneumococcus meningitis. He died on the following day. No autopsy.

Case 17—M H, a white female, age 14 months, was admitted to the Babies Hospital with a history of jaundice, clay colored stools and dark urine since birth. Development had been normal and she had had no digestive disturbance. Deeply jaundiced infant weighing 16 pounds. The liver was very large and nodular. The spleen was enlarged. R B C 2,500,000, Hb 40 per cent, fragility of the red cells was

ATRESIA OF BILE DUCTS

normal, Kahn and tuberculin were negative. Van den Bergh immediate, direct was positive, urine positive for bile and the stools bile negative. She was transfused twice in preparation for operation. Twenty-four hours after the second transfusion she developed a fever and vomited a large amount of bright red blood. She was transfused again but continued to raise small amounts of bright red blood for the next ten days. On the eleventh day she suddenly went into shock and died, apparently from a large gastrointestinal hemorrhage. No autopsy. We had every reason to believe that this patient had congenital atresia of the bile ducts, yet she was 14 months of age at death. It is very unusual for these patients to survive this long.

Case 18—R. C., a male, age six weeks, was admitted to the Babies Hospital with a history of jaundice and dark colored urine since two weeks of age. The stools during this period were said to have been colored occasionally. He was poorly nourished, deeply jaundiced, with a liver just palpable below the costal margin. The spleen was not felt. The first stool in the hospital was colorless. The urine was positive for bile, the stools bile negative except on one occasion when a stool which was contaminated by urine gave a

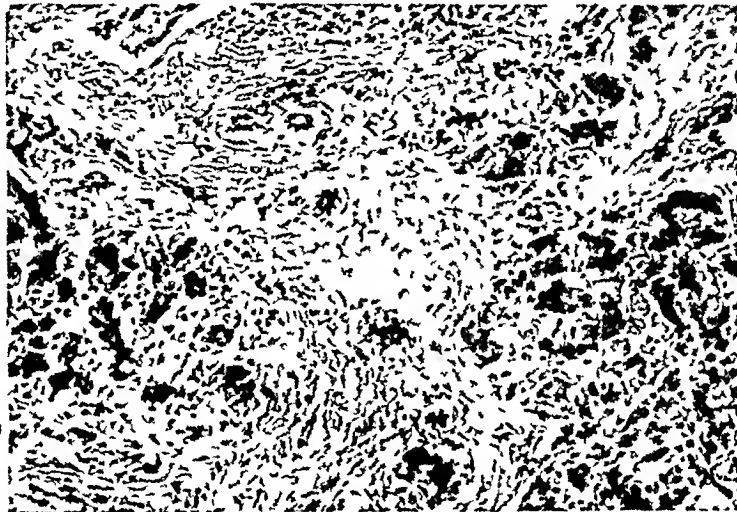


FIG. 2.—Photomicrograph of the liver showing the degree of cirrhosis present at time of death in congenital atresia of bile ducts.

positive test for bile. The fragility of the red cells was normal, bile index 25, van den Bergh immediate, direct positive. At operation all tissues were deeply bile stained, the liver was large, firm and dark green in color. The gallbladder was small, colorless and empty, the common and hepatic ducts were like fibrous cords and seemed completely closed. The abdomen was closed as it seemed that surgery could not help the condition. His convalescence was uneventful and he was discharged 14 days after operation. During the latter part of his hospital stay, a rash was noticed on the neck, chest, abdomen and on the flexor surface of his fingers. He returned to the clinic ten days after discharge, when it was noted that the jaundice was less. Two weeks later the jaundice appeared still less marked and while the stools were said to be yellow, the urine was still very dark. One month later (about ten weeks after operation), the jaundice had about disappeared and cholesterol deposits were seen at the sites of the rash which he developed shortly after operation. At this time the van den Bergh was still positive but the urine was bile negative. Total cholesterol 1,215, free 589, combined 686, ratio c/f 1.06. This patient was last seen on April 13, 1937, about two and one-half years after operation, and was quite well except for the skin lesions, which have been diagnosed as xanthomatosis. I do not know how to explain the outcome of this case as regards the bile ducts. It seemed evident at operation that the obstruction of the ducts was at or near the portal fissure since the ducts appeared as fibrous cords. The result in this case was similar to that in Case 2.

SUMMARY

(1) Eighteen cases of congenital atresia of the bile ducts are reported. There were nine males and nine females.

(2) Icterus in a newborn child, which persists for more than three weeks, with clay colored stools, bile in the urine and a positive, immediate direct van den Bergh reaction, justifies the diagnosis of congenital atresia of bile ducts.

(3) The aim of surgery in these cases is to deliver the bile into the intestinal tract.

(4) In only one case in this group was there enough of the bile duct system present to make corrective surgery possible.

(5) Two cases (Nos. 2 and 18) thought to have complete obliteration of the bile ducts at operation are alive and well two and one-half and three years after operation.

(6) These cases all deserve an exploratory celiotomy in the hope that there is enough of the duct system developed to make surgery worth while.

(7) Complete obliteration of the bile ducts is invariably fatal, usually before the age of six months.

REFERENCES

- ¹ Altschule, M. D. Vitamin Deficiency in Congenital Atresia of the Bile Ducts. *Arch Path*, **20**, 845, 1935.
- ² Cole, W. H. Congenital Malformation of the Bile Ducts and the Intestinal Tract in Infancy. *Arch Surg*, **23**, 820, 1931.
- ³ Croswell, C. V. Congenital Absence of the Extrahepatic Ducts and Gallbladder. *J Tenn Med Assn*, **27**, 316, 1934.
- ⁴ Danzis, M. Congenital Absence of the Gallbladder. *Am J Surg*, **29**, 202, 1935.
- ⁵ Deaver, J. M. B. Congenital Absence of the Extrahepatic Ducts and Gallbladder. *Am J Dis Child*, **46**, 356, 1933.
- ⁶ Gross, R. E. Congenital Anomalies of the Bile Ducts. *Arch Surg*, **32**, 131, 1936.
- ⁷ Holmes, J. B. Obliteration of the Bile Ducts. *Am J Dis Child*, **11**, 405, 1916.
- ⁸ Howard, C. D., and Wolbach, S. B. Congenital Obliteration of the Bile Ducts. *Arch Int Med*, **8**, 557, 1911.
- ⁹ Keith, T. S. Congenital Obliteration of the Bile Ducts. *Proc Roy Soc Med*, **25**, 1735, 1932.
- ¹⁰ Kirshbaum, J. D. Congenital Absence of Gallbladder and Extrahepatic Ducts. *Am J Dis Child*, **47**, 1080, 1934.
- ¹¹ Latoe, E. W. Congenital Absence of the Bile Ducts. *J Indiana Med Assn*, **27**, 373, 1934.
- ¹² Ladd, W. E. Congenital Atresia of the Bile Ducts. *J A M A*, **91**, 1082, 1928; Congenital Obstruction of the Bile Ducts. *ANNALS OF SURGERY*, **102**, 742, 1935.
- ¹³ McClendon, S. J., and Graham, H. K. Congenital Atresia of Hepatic Duct. *Arch Pediat*, **48**, 791, 1931.
- ¹⁴ Montgomery, A. H. Congenital Obstruction of the Bile Ducts. *Surg Clin N Amer*, **16**, 93, 1936.
- ¹⁵ Parsons, L. G., and Herkman, E. M. Biliary Cirrhosis. *Am J Dis Child*, **31**, 459, 1926.
- ¹⁶ Scriver, J. B. Congenital Absence of Hepatic and Common Ducts. *Canad M A J*, **27**, 517, 1932.
- ¹⁷ Sweet, L. K. Congenital Malformation of the Bile Ducts. *J Pediat*, **1**, 496, 1932.
- ¹⁸ Watkins, A. G., and Wright, G. P. Congenital Atresia of Bile Ducts. *Lancet*, **1**, 1066, 1933.

OBSTRUCTIVE JAUNDICE

THE CAUSE AND PREVENTION OF THE BLEEDING DYSCRASIA²

HOWARD C NAFFZIGER, M D , JESSE L CARR, M D , AND
FREDERICK S FOOTE, M D

SAN FRANCISCO, CALIF

FROM THE DEPARTMENTS OF SURGERY AND PATHOLOGY OF THE UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL,
SAN FRANCISCO, CALIF

For the past several years, we have been interested in the cause and prevention of the bleeding dyscrasia of obstructive jaundice. We conducted, on animals, a series of experiments in which jaundice was produced mechanically. Observations were made on the blood of these animals at all stages of the disease in an attempt to reveal deficiencies in the clotting elements. Similar observations were made on the blood of jaundiced patients being treated in the University hospitals.

Recently the dietary approach to the problem of the bleeding diathesis in obstructive jaundice has been opened and a relation established between certain foods and the production of prolonged coagulation and bleeding times with spontaneous hemorrhage.

Immature chickens, when fed on a diet consisting mainly of dried fish meal, develop such a marked tendency toward bleeding that they bleed to death from trivial wounds.¹ Cattle fed on sweet clover hay, which has been allowed to ferment, lose their normal power of coagulation and may suffer fatal hemorrhage within a period of 48 hours after the diet is started.¹

Human beings who ingest certain organic sulphur compounds, the products of normal metabolism of protein, exhibit a prolonged coagulation and bleeding time for hours thereafter.² The mechanism of this inhibition of proper clotting is not clearly explained. In each condition, however, it has been reported that there is a deficiency in either the quality or the quantity of the prothrombin of the blood.³ As prothrombin (Chart 1) is a theoretic sub-

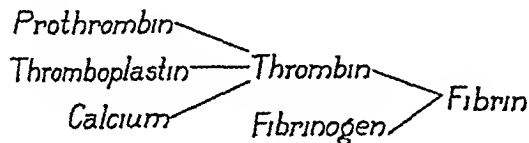


CHART 1—A diagrammatic representation of
Howell's theory of coagulation

stance essential for clotting, which remains in the plasma after the other known factors are removed, its deficiency cannot be definitely assigned as quantitative or qualitative. The presence of an anticoagulant might also explain this deficiency, even in the presence of normal prothrombin. Such an effect upon

* This work has been conducted under grants from the Christine Breon Fund for Medical Research and from the Research Budget of the Department of Pathology of the University of California Medical School, San Francisco, Calif.

the prothrombin could be caused by an intoxication resulting from the excessive absorption of certain food products, and there is very good evidence to show that this is the case when organic sulphur compounds such as cystine and methionine are fed. In the human being, the effect upon the coagulation time, of the administration of slightly over a gram of methionine, has been to prolong the coagulation time from four to 15 minutes in a period of two hours.² The administration of the same amount of methionine intravenously has a slightly greater effect in the same period of time.² Similar results are obtained from the administration of taurine and taurocholic acid.² In 1934, we suggested that the blood of jaundiced patients contained an anticoagulant which, in certain cases, was sufficiently concentrated to account for the deficient clotting power and the resultant hemorrhagic diathesis.⁴

Knowing that normal human bile contains the anticoagulant cysteine, we suspected that, in the presence of a block of the common duct, this substance, as such, or as taurine, taurocholic acid, or other more simple combinations, might be retained in the circulating blood in sufficient quantities to effect coagulation.

Dogs, in which jaundice had been produced by ligation and division of the common bile duct, were fed exclusively on meat which is rich in cystine. All of these dogs suffered from hemorrhages of the bowel and many died as a direct result of bleeding (Chart 2). Jaundiced dogs given a diet of bread, milk and vegetables lived on an average of three times as long as those given meat alone, and only half of them suffered from hemorrhage. Organic sulphur compounds were detected in the whole plasma of the jaundiced animals in increasing concentration as the disease progressed. The same was true of the blood of jaundiced human beings. The tests were made by the sodium nitroprusside method, which is rather crude when adapted to blood plasma, and yields only gross color changes with no quantitative results.

The observations to be reported herewith were made from experiments devised to prove the presence and the anticoagulant action of sulphydryls in the blood of jaundiced animals and human beings. Dogs were chosen as experimental animals because they subsist on a diet similar to that of man and their bile is similar to human bile.

Jaundice was produced in dogs by ligation and division of the common bile duct. The blood was analyzed for its sulphur content before operation and at regular weekly intervals after operation until death. The dogs were fed a regular diet of meat, bread, potatoes and green vegetables. Each specimen of blood was taken after 24 hours of fasting.

The plasma proteins were digested with hydrochloric acid and the total sulphur determined by the benzidine sulphate titration method.⁵ Chart 3 shows the average total plasma sulphur of the blood of two normal control animals over a period of six weeks. The total amount of sulphur varied between 65 and 75 mg per 100 cc with an average of approximately 70 mg.

Chart 4 shows the effect of jaundice upon the total plasma sulphur. Curve II of Chart 4 shows an average total increase in sulphur in the plasma of

OBSTRUCTIVE JAUNDICE

seven jaundiced dogs from 70 to 90 mg per 100 cc in four weeks. The total amount of sulphur in the blood of the one animal which died of hemorrhage rose from 55 mg to nearly 100 mg per 100 cc in two weeks. The amount of sulphur decreased during the last week or two of life, possibly because of

RELATION OF DIET TO SURVIVAL PERIOD
AND INCIDENCE OF HEMORRHAGE

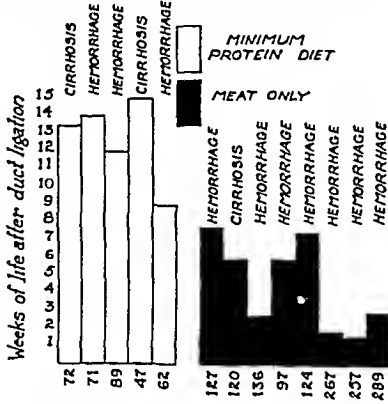


CHART 2—Illustrates the effect of a diet high in protein upon the period of survival and the incidence of hemorrhage in jaundiced animals. Each column represents one jaundiced dog. The white columns represent dogs given a low protein diet and the black columns those which were given meat only. The cause of death is indicated above each column.

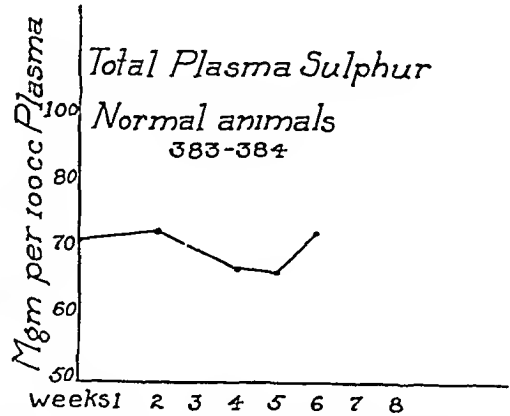


CHART 3—The total plasma sulphur of two normal animals remained at approximately 70 mg per 100 cc for a period of six weeks.

hemorrhage and dilution of the blood. The total amount of sulphur in the plasma of six deeply jaundiced patients was determined (Chart 5). It ranged from slightly above normal to almost twice normal.

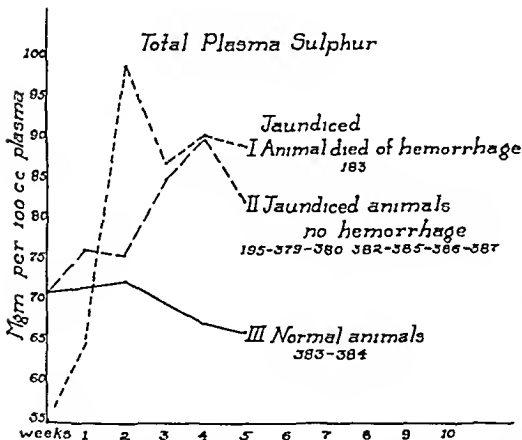


CHART 4—Shows the rapid rise of the total plasma sulphur in jaundiced animals. An animal which died of hemorrhage shows the most marked rise.

Plasma Total Sulphur of Jaundiced Patients

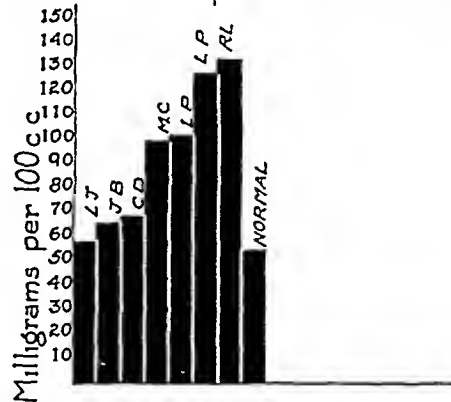


CHART 5—Each column represents the total sulphur level of the whole plasma of a jaundiced patient as compared with the average normal. One patient (L P) with a total of 125 mg per 100 cc died of hemorrhage following removal of a stone in the common duct.

It seems apparent that most of the accumulated sulphur is combined with, or closely associated with, the plasma protein because the protein free plasma does not show the same marked variation in total sulphur content that the whole plasma does.

Chart 6 shows the effect of jaundice on the level of the total amount of

sulphur in the protein free plasma. These analyses were made upon specimens of plasma from which the proteins had been precipitated. It can be seen that there is no definite characteristic change except perhaps in those dogs which died of hemorrhage and in which are shown a moderate terminal rise and then, with the inception of fatal hemorrhage, a final drop.

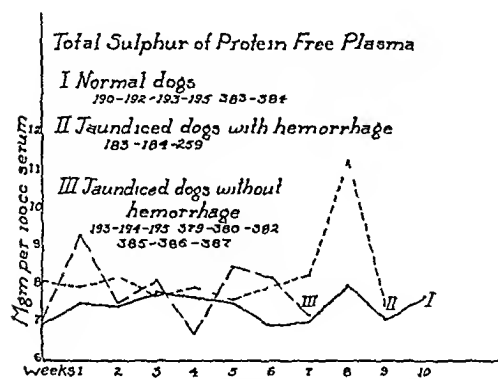


CHART 6—Illustrates the fairly constant level of sulphur content of plasma from which the proteins have been precipitated. The dogs which died of hemorrhage show a sharp terminal rise then a drop with the inception of hemorrhage.

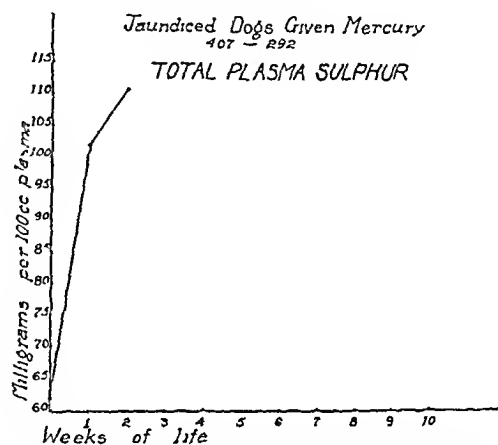


CHART 7—Two jaundiced dogs poisoned with mercury evidence a more rapid rise in total plasma sulphur than those without mercury. Their period of survival was very short, being less than three weeks.

The rapid rise in blood sulphur following ligation of the common duct is not entirely the result of that block but is secondarily dependent on the condition of the kidneys. Chart 7 shows the accelerated rise during the short survival of two dogs given, intramuscularly, 0.05 mg of mercury per kilogram of body weight twice a week.

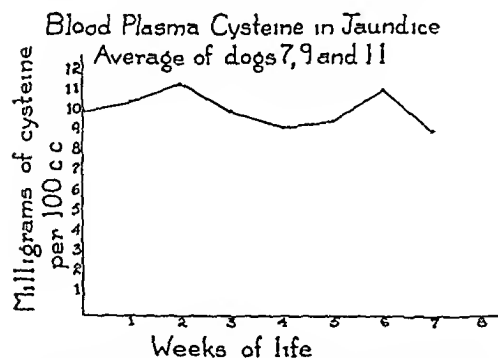


CHART 8—Illustrates the fairly constant level of blood plasma cysteine with the onset and progress of obstructive jaundice.

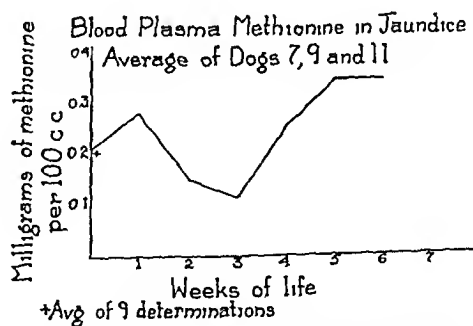


CHART 9—There is considerable fluctuation in the level of total plasma methionine from week to week but the general trend is upward with the progress of the jaundice. In the final stages of the disease the level is almost twice normal.

Specific analyses for cystine were carried out by an adaptation of Baernstein's⁶ iodine titration method for determination of the distribution of sulphur in proteins. The cysteine content of the plasma remained at a constant and normal level throughout the disease (Chart 8). The methionine content varied a great deal from week to week (Chart 9) but, at an advanced stage of the disease, it increased to nearly 4 mg per 100 cc.

DISCUSSION —These and other experiments have established the fact that, in the presence of jaundice, there is an alteration in the sulphur metabolism of animals and human beings. An important feature of this alteration is the retention in the circulating blood of sulphur compounds which are anticoagulants. That only minute quantities need be retained to alter coagulation is shown by the fact that small doses of the purified product, such as cysteine or methionine, produce a marked effect *in vivo*,² and minute amounts will alter coagulation *in vitro*.¹

An important secondary feature affecting the concentration of these products is the condition of the kidneys. Sulphur compounds normally excreted by the liver as cystine, taurine and taurocholic acid are shunted through the kidneys. The sudden rapid rise in blood sulphur with the onset of jaundice in animals given mercury showed experimentally that the threshold for excretion of these products is raised by damage to the kidneys.

Clinically it is well known that a jaundiced patient's chances of survival are jeopardized by poorly functioning kidneys and that jaundiced patients given mercury compounds such as salyigen are particularly likely to bleed.

That the source of the anticoagulant material is metabolized protein, both exogenous and endogenous, is shown by the fact that jaundiced dogs fed meat alone on which normal dogs thrive, lived only one-third as long as those allowed a minimum of protein, and nearly all succumbed to massive hemorrhage. It seems important that, in patients with obstructive jaundice, the intake of protein should be kept at a minimum during the period of preparation for surgery. Furthermore the metabolism of body proteins should be minimized by rest in bed and the administration of sedatives.

Feeding of excess carbohydrate and the administration of glucose intravenously decrease the metabolism of protein. The output of bile salts from a biliary fistula is reduced to a low level when the animal is starved, but it is still further reduced when carbohydrate only is fed.⁷ That the giving of glucose has other important beneficial effects than these is not doubted.

An excess of calcium chloride appreciably inactivates sulphhydryl anticoagulants *in vitro*.⁴ Its use in patients with jaundice is based on the belief that it has the same effect *in vivo* if it is administered in sufficient quantity.

The benefit to be derived from infusion of normal blood is obvious, but the difficulty of replacing a sufficient quantity of blood presents itself.

CONCLUSIONS

(1) The blood plasma content of sulphur compounds is increased in obstructive jaundice in dogs and in man.

(2) It is possible that, in jaundice, the defect in coagulation is caused by retention in the blood of certain of the organic sulphur compounds which are anticoagulants.

(3) The metabolism of these sulphur compounds can be minimized—the exogenous by a minimum maintenance diet of protein, and the endogenous by

complete rest and the use of large amounts of carbohydrate by vein and in the diet

REFERENCES

- ¹ Quick, A J The Coagulation Defect in Sweet Clover Disease and in the Hemorrhagic Chick Disease of Dietary Origin *Am J Physiol*, 118, No 2, 260-271, February 1, 1937
- ² Sterner, J H, and Medes, Grace The Effect of Certain Sulfur Compounds on the Coagulation of the Blood *Am J Physiol*, 117, No 1, 92-101, September 1, 1936
- ³ Quick, A J, Brown, M S, and Bancroft, F W A Study of the Coagulation Defect in Hemophilia and Jaundice *Am J Med Sci*, 190, 501-511, 1935
- ⁴ Carr, J L, and Foote, F S Progressive Obstructive Jaundice *Arch Surg*, 29, 277-296, August, 1934
- ⁵ Wakefield, E G The Colorimetric Determination of Total and Inorganic Sulphates in Blood Serum, Urine and Other Body Fluids *J Biol Chem*, 81, 713-721, 1929
- ⁶ Baernstein, H D The Sulphur Distribution in Proteins The Combined Methods for the Determination of Cysteine, Methionine, and Sulphates in Hydriodic Acid Digests *J Biol Chem*, 115, 33-37, 1936
- ⁷ Smith, H P, Groth, A H, and Whipple, G H Bile Salt Metabolism *J Biol Chem*, 80, 659-669, 1928

DISCUSSION —DR WALTMAN WALTERS (Rochester, Minn) I want to compliment Doctors Naffziger, Foote, and Carr for their excellent studies on the chemistry of the changes in coagulation in cases of obstructive jaundice. I think their discovery of these abnormal products of protein metabolism confirmed what many of us have thought to be true in the case of the patient with obstructive jaundice who has abnormal function of the liver. They have shown in these studies, which have been well controlled, the efficacy of intravenous injections of glucose and of blood transfusions.

For a good many years following the work of Opie and of Mann, and more recently of Ravdin, it has been recognized clinically that probably the most important method we have of assisting the liver to function when the patient has obstructive jaundice is by the use of blood transfusions and glucose intravenously. From the surgical standpoint, however, it is not only necessary to replace, so to speak, some of the metabolic substances which the abnormally functioning liver lacks in production, but it is also equally important to relieve completely the biliary obstruction at the time of operation. I am sure that many of us have been worried subsequent to operation for biliary obstruction when, because of the nature of the lesion, which is usually a malignant one of the ducts, located high, and when it was impossible to relieve the obstruction, we have seen the patient bleed to death in spite of everything that we could do in the way of replacement chemotherapy. Quite obviously in such cases the bleeding was the result of continued failure of liver function. The function of the liver, after all, determines whether the jaundiced patient is going to recover.

It has been a matter of regret to many of us to find how occasionally after the successful removal of an obstructive lesion of the common bile duct that the patient has failed to recover. In our experience at the Mayo Clinic, however, during the past 15 years, bleeding has played a very minor rôle. As a matter of fact I have just gone over the statistics at the Clinic for last year (1936) and I find that among 209 jaundiced patients who were operated upon, that is, jaundiced patients with lesions of the biliary tract, there were only two deaths from hemorrhage. On the other hand, there were deaths from other causes, for the mortality was 35 per cent. The other deaths were, for the most part, from pulmonary embolism and bronchopneumonia.

Personally I believe that the control of these two lethal factors is of the utmost importance in lowering the risk of operative procedures, not only in the case of jaundiced patients, but in those in which patients are operated upon for other intra-abdominal lesions

I think the value of the study of the constituents of the blood that Doctor Cain has described is exceedingly important. The test of blood coagulability, as described by Doctor Bancroft and his associate, Doctor Stanley-Brown, has been of the greatest aid to us in determining liver function. As a matter of fact, in cases of jaundice I believe it is one of the most important indexes of liver function both prior and subsequent to operation.

Nygaard and Baldes have modified the method by using a photo-electric cell, and they have been able to show that there is a definite curve of the rate of coagulation which can be demonstrated by physical methods. The jaundiced patients' curve will taper off from the curve of the normal rate of coagulability. This evidence of retardation of blood coagulation, and the three phases of coagulation are accurately recorded. I have seen jaundiced patients, who apparently subsequent to operation were doing well, who had curves of this type and in whom, two or three days later, bleeding occurred.

I want to compliment Doctor Naftziger and his colleagues again on this excellent piece of work. It adds a very important chapter to the study of the chemical changes associated with hepatic dysfunction.

DR ROSCOE R. GRAHAM (Toronto, Canada) One of the greatest difficulties we have encountered in the preoperative preparation of patients suffering from obstructive jaundice is to determine where the optimum improvement has been attained. Until the method of determining bleeding time as suggested by Ivy and his associates became a part of our preoperative regimen, we had no confidence in our ability to prophesy which patients would suffer from postoperative hemorrhage. The method suggested by Ivy consists in applying a blood pressure cuff on the upper arm, raising the pressure to 40 Mm of mercury, and maintaining it for one minute prior to making a 2 Mm puncture on the forearm. With the pressure maintained at 40 Mm, the upper limit of bleeding in a normal individual was estimated to be four minutes.

During the last two years we have been forced to operate upon only one patient where the bleeding time, as determined by this method, exceeded four minutes. This is the only case in this series in which we encountered serious postoperative bleeding. In previous cases where postoperative hemorrhage occurred, it was noted that such rarely took place before the seventh or eighth postoperative day. We now give on the fifth postoperative day, a transfusion of 500 cc of citrated blood, even though the patient's progress and condition seem satisfactory. We have thus been able to determine the optimum time to undertake the operation, and have added to the safety of the procedure by this regimen.

DR DANIEL F. JONES (Boston) I should like to call attention to the fact that it has been shown that the kidney function apparently has a definite influence in instances of bleeding dyscrasia, and that the most serious cases in which this phenomenon has been evidenced have occurred in patients whose kidney function has been markedly diminished. In a comparatively recent case, the patient had been jaundiced for only ten days, and yet bled to death, notwithstanding the administration of five transfusions. The consideration of this fatality caused us to conclude that the continued bleeding was caused by the fact that the kidney function was very low. It, therefore, may be well to take into consideration the kidney, as well as the liver function, in combating the etiologic factor, causative of the bleeding dyscrasia in these cases.

MORTALITY IN ACUTE ILEUS

STATISTICAL REPORT OF FOUR HUNDRED FIFTY CASES OPERATED UPON
AT THE PRESBYTERIAN HOSPITAL, NEW YORK

FREDERICK T VANBEUREN, JR, M D, AND BEVERLY C SMITH, M D
NEW YORK

FROM THE DEPARTMENT OF SURGERY COLUMBIA UNIVERSITY AND THE SURGICAL SERVICE OF
THE PRESBYTERIAN HOSPITAL NEW YORK, N Y

TEN years ago, the authors¹ began a study of the results of operation for acute ileus based upon mortality statistics, with particular reference to the value of enterostomy. It was shown in that report that the average mortality in acute ileus following operations upon that condition at seven different hospitals had fallen only 2 per cent in 25 years, although the mortality at the various hospitals varied very considerably. It was also shown that the mortality in such cases which were treated by enterostomy had been reduced only 4 per cent during the same period.

In summarizing, the authors stated, in part "The actual value of enterostomy as a treatment for acute ileus must be determined ultimately by statistical proof. Statistics published up to this time do not afford a satisfactory basis for comparison, except in a few instances, too few for definite conclusions. Because of the recognized effect that early operation has on the mortality in this condition, any series of acute ileus cases (in order fairly to compare its results with those of another series) must be analyzed into its component group of early and late cases." In another report,² the importance of this time element was further emphasized.

The study, the progress of which has, therefore, been twice previously reported on, has been continued through the year 1935, and the 20 year results are herewith reported. The 20 year analysis has been divided into five periods of four years each, in order to test whether improvement in results (if found) was progressive or not. Table I shows the comparison thus made.

TABLE I

MORTALITY PERCENTAGES IN 450 CASES OF ACUTE ILEUS OPERATED UPON AT THE PRESBYTERIAN HOSPITAL (INCLUDING PARALYTIC AS WELL AS MECHANICAL TYPES) FROM 1916 TO 1935

Compared by Four Year Periods

Whole Series

1916-1919 inc	Total cases = 60 (81% late)*Mortality = 66.6%
1920-1923 inc	Total cases = 80 (66% late) Mortality = 53.7%
1924-1927 inc	Total cases = 108 (61% late) Mortality = 44.4%
1928-1931 inc	Total cases = 72 (71% late) Mortality = 48.6%
1932-1935 inc	Total cases = 130 (60% late) Mortality = 28.4%
	450
	752

45.1%

MORTALITY IN ACUTE ILEUS

Enterostomy Group

1916-1919 inc	Total cases = 22 (64% late)	Mortality = 90.9%
1920-1923 inc	Total cases = 38 (79% late)	Mortality = 78.9%
1924-1927 inc	Total cases = 75 (73% late)	Mortality = 53.3%
1928-1931 inc	Total cases = 51 (74% late)	Mortality = 56.8%
1932-1935 inc	Total cases = <u>64</u> (77% late)	Mortality = <u>42.2%</u>
	250	58.4%

Nonenterostomy Group

1916-1919 inc	Total cases = 38 (92% late)	Mortality = 52.6%
1920-1923 inc	Total cases = 42 (55% late)	Mortality = 34.0%
1924-1927 inc	Total cases = 33 (33% late)	Mortality = 24.2%
1928-1931 inc	Total cases = 21 (48% late)	Mortality = 28.6%
1932-1935 inc	Total cases = <u>66</u> (40% late)	Mortality = <u>15.1%</u>
	200	29.0%

*"Per cent late" in parentheses means the percentage of cases (in the series or group) in which more than 48 hours had elapsed between the onset of the symptoms and the time when operative relief was undertaken

COMMENTS ON TABLE I

(1) It must be emphasized that each of these four year series includes all the cases of acute ileus operated upon at this hospital, during the period, whether of mechanical or paralytic type. The inclusion of the paralytic type (peritonitis ileus) undoubtedly increases the mortality percentage, as does the inclusion of carcinoma cases.

(2) It must also be noted that this is not the report of a single surgeon, particularly skilled in the management of such cases. The operative work was performed by the Surgical Staff of the Presbyterian Hospital, including about 20 surgeons.

(3) Table I shows a steady reduction in mortality from one four year period to another with the exception of the fourth period (1928 to 1931, inclusive). It was at the beginning of this period, in April, 1928, that the Presbyterian Hospital moved to its new location, five or six miles farther uptown and the local physicians had not yet acquired the habit of sending in cases early. This perhaps accounts for the fact that that period had a higher percentage of late cases (71 per cent) than the period immediately preceding it (1924 to 1927, inclusive). It will be seen also that in that same period (1928 to 1931, inclusive) a much larger proportion of the cases had enterostomy performed (51 enterostomies to 21 nonenterostomies), indicating that they were considered more seriously ill. These two factors are probably responsible for the higher mortality in that period than in the period immediately preceding it.

(4) Although the reduction in mortality has been steadily maintained by four year periods (with the exception noted above) the general mortality for the entire 20 year period is about 45 per cent—decidedly too high.

(5) It is, therefore, particularly encouraging to find the mortality (28.4

per cent) for the most recent period (1932 to 1935, inclusive) so notably lower than the preceding periods. This reduction cannot be ascribed to the time element because there was only 1 per cent fewer late cases than in the period 1924 to 1927, inclusive. Credit must be given in large part to the better management of the cases.

(6) Observing the results of the first and last four year series, in connection with the two groups which make up each series, it is seen that the mortality of the 1932 to 1935 series is a little less than one-half that of the 1916 to 1919 series, and that the mortality of the 1932 to 1935 enterostomy group is also a little less than one-half that of the 1916 to 1919 enterostomy group. In other words, the mortality reduction is approximately equal in the series and in the enterostomy group. In the nonenterostomy group, on the other hand, the mortality of the 1932 to 1935 group is less than one-third of that of the 1916 to 1919 group. The reduction in this group is thus much greater than that secured in the series or in the other group.

(7) This observation is impossible to explain unless one takes the time element into consideration. Considering this also, it is seen that the last series had 21 per cent fewer late cases than the first series, while the last nonenterostomy group had 52 per cent fewer late cases than the first nonenterostomy group. The time element, therefore, is partly responsible for the greater improvement in that group.

(8) The time element cannot, however, be the only controlling factor in reducing mortality. Better technic, better surgical judgment and better management of cases must also play a part. We find confirmation of this in studying the enterostomy four year period groups. The last enterostomy group (1932 to 1935) has a mortality less than one-half that of the first group (1916 to 1919) *in spite of the fact that it includes nearly 13 per cent more late cases* than the first group. Moreover, its mortality is lower than that of the other two enterostomy groups (1924 to 1927 and 1928 to 1931), each of which had fewer late cases. These observations seem to indicate that improvement in technic, judgment and management has had a strong influence in reducing mortality in enterostomy cases.

(9) Contrasting the results of cases which have had an enterostomy added to the relief operation with those which have not, it is seen that the mortality is much lower in the latter than in the former. In the first four periods shown in Table I, the mortality of each nonenterostomy group is just about one-half that of the corresponding enterostomy group, while, in the last period, it is only about one-third that of the last enterostomy group.

(10) This does not necessarily mean that enterostomy is a dangerous procedure. It does mean that it is not the cure-all that certain writers have represented it to be. One sees that it is, in general, performed more often in late than in early cases and one knows that their chances of recovery are, in general, less—whether or not they have an enterostomy added to their other operation—than in the early cases. For example, there were (in the

MORTALITY IN ACUTE ILEUS

1932 to 1935 series) 52 early cases (operated upon within 48 hours) with an average mortality of only 15.3 per cent, while in the 78 late cases (operated upon after 48 hours) the average mortality was 39.7 per cent, irrespective of whether or not they had an enterostomy. And it must be kept in mind that no enterostomy would have been added if the case had not been considered sufficiently serious to require it. Our feeling is that enterostomy has been a valuable adjunct in many of the cases in which it was effected.

(11) But enterostomy is by no means always helpful and it *must* be used with judgment. Overenthusiasm about it is unjustifiable. For there is little use in performing an enterostomy in a bowel which has lost its contractibility either through prolonged overdilatation or peritonitis toxemia.

CONCLUSIONS

(1) Within a period of 20 years the average mortality of acute ileus cases operated upon at the Presbyterian Hospital, New York, has been reduced from 66.6 per cent (1916 to 1919, inclusive) to 28.4 per cent (1932 to 1935, inclusive).

(2) This reduction in mortality percentage has been gradual and regularly progressive (as compared by four year periods), with the exception of one period, following the hospital's removal into a new district, when the cases were received later than usual.

(3) The improvement applies to the cases upon whom an enterostomy was effected as well as to those upon whom it was not done, but the reduction in mortality was much greater in the nonenterostomy group than in the enterostomy group. This discrepancy appears to be in part due to the fact that, in general, the nonenterostomy group were operated upon earlier than the enterostomy group.

(4) The three factors chiefly responsible for this reduction in mortality percentage appear to be

- (a) Earlier diagnosis and operation
- (b) A clearer conception of the problem to be solved by treatment
- (c) More intelligent handling and management of the cases

REFERENCES

- ¹ vanBeuren, Frederick T, Jr, and Smith, Beverly C. The Status of Enterostomy in the Treatment of Acute Ileus. *Arch Surg*, 15, 288-297, August, 1927.
- ² vanBeuren, Frederick T, Jr. Mortality of Enterostomy in Acute Ileus. Improvement Not Referable to the Time Element. *Tr Southern Surg Assoc*, 41, 283, 1928.

PERINEPHRIC ABSCESS

RICHARD H. MILLER, M.D.

BOSTON, MASS.

THE subject of perinephric abscess is a very interesting one, and lies quite as much within the realm of the general surgeon as of the urologist. It is one of those border-line lesions which are so baffling. In fact, what led to the writing of this paper was the observation of several cases in which the surgeon and the urologist were in entire disagreement about the diagnosis, which was not made until exploratory operation was performed. Errors in diagnosis are frequent, and these errors are made, in the early stages, because the local symptoms and signs may be minimal or absent, and, in the later stages, because there are so many lesions that may be confused with each other. The cases at the Massachusetts General Hospital were carefully studied by Richardson¹⁵ in 1915, and Swan¹⁹ in 1933. The object of this paper, which has fewer cases to present than either of the two above-mentioned authors, is to again call to the attention of the general surgeon the importance of this lesion.

Surrounding the kidney parenchyma is a capsule, outside of which is a layer of fat, this, in turn, is enclosed in a loose fibrous sheath, the "fascia renalis," with another fatty layer outside it. It has been suggested that one may speak of the inner fatty layer as the "perirenal," and the outer as the "pararenal." At the lower pole the fascial layers of the sheath do not coalesce, but continue downward, separately, toward the iliac fossa. The blood supply of the perinephric area is from terminal branches of the lumbar arteries, arising from the aorta, and from the perirenal twigs from the renal arteries. These two terminal divisions anastomose.⁸ It is thus clear that, if the infection be blood-borne, it may come from the lumbar vessels, without traversing the kidney, it may come through the renal arteries to the perirenal space without stopping in the kidney, or, obviously, it may have localized in the periphery of the kidney and thence perforated through the capsule into the perirenal fat.

Perinephric abscess, in the ordinary acceptance of the term, is, like osteomyelitis, a local area of infection secondary to a focus elsewhere in the body, most commonly in the respiratory tract. A perinephric abscess, resulting from the perforation of a cortical renal abscess, may, however, not be distinguishable from the purely blood-borne type. Cabot⁴ speaks of the intimate relation of the pyogenic blood stream infections which result in massive abscess of the kidney, multiple abscesses of the kidney, perinephritis, "and its offspring, perinephritic abscess." Whether the perinephric infection be due to, or independent of, an antecedent renal infection, the cardinal features of the condition, and the indications for treatment, are

practically the same. The ordinary pus producing cocci are the most common infecting agents.

Usually the symptoms calling attention to the lesion develop within two to four weeks after the original focus of infection has been noted. There may be nothing to direct one's attention to the kidney region, the patient presenting only fever, malaise, elevated white count, and frequently a negative urine. After the abscess has had time to develop in size, there may be a vague sense of discomfort in the renal area—very rarely acute pain. In one of our cases (a feebleminded boy of 16) the first thing noted was that the patient assumed, on standing, an abnormal posture, with flexion of the hip on the involved side.

In arriving at a diagnosis, the first thing is that one must always think of this condition in cases of unexplained fever of a duration of a week or more. Careful inspection, the physician standing at the foot of the bed, the patient supine and uncovered down to the pubes, may reveal slight limitation of the respiratory excursion on the affected side. In advanced cases a definite bulge, under the costal margin and in the flank, may be detected, and vague tenderness and discomfort may be elicited on local bimanual examination.

Cystoscopic examination is usually negative. Pyelography reveals, in perinephric abscess, a general dislocation of the kidney, in massive abscess of the kidney a deformity of the calices may be seen. Although the ordinary uranalysis is negative, careful examination by smear and culture of a centrifuged urine specimen will frequently reveal pyogenic cocci.¹⁻⁴ Cabot⁴ examined in this way the urine in 46 cases of perinephric abscess, of these, 32 showed positive smears and 18 showed positive cultures. This diagnostic method should be tried, when possible, in all doubtful cases.

In the absence of other suggestive data, the roentgenologic examination offers today the most valuable aid in diagnosis, as is attested by the studies of many authors.^{18-20, 21} In a series of 40 cases studied by Shane and Harris,¹⁸ there was some obliteration of the psoas shadow in 100 per cent, some change in the kidney shadow in 80 per cent, and some degree of scoliosis in 45 per cent. In 32 cases there was elevation of the diaphragm in 28 per cent. There may be decreased definition of the shadows of the transverse processes of the lumbar vertebrae on the affected side.²¹ Fluoroscopy may reveal some limitation of the excursions of the diaphragm.⁴

It is, then, important to remember, that in any case of suspected perinephric abscess, or in any case of long unexplained fever, it becomes imperative to do a bacteriologic examination (both by smear and culture) of centrifuged urine, and a roentgenologic examination of both kidney areas.

The problem of differential diagnosis offers many interesting facts and suggestions. Rusche and Bacon¹⁶ present a study of ten cases diagnosed as perinephric abscess (nine were operated upon) and in every instance the diagnosis was wrong. This report is so interesting that their findings

are here listed and then original article should be studied The ten cases which were diagnosed perinephric abscess proved to be

Appendiceal abscess	2
Osteomyelitis of rib	1
Osteomyelitis of rib and vertebra	1
Osteomyelitis of vertebra	1
Hydronephrosis, ruptured	1
Abdominal aneurysm, ruptured	1
Perforation of intestine by foreign body	1
Perforated carcinoma of intestine	1
No pathology	1

Swan¹⁹ lists 29 conditions which have been mistaken for perinephric abscess Early age does not rule out perinephric abscess, as one case is reported that was only five and one-half years old³ Deane reports one case of "empyema necessitatis" which simulated this condition Nesbit and Keene,¹⁴ discussing 60 cases from the University Hospital, Ann Arbor, report six cases of perinephriobronchial fistula, stating that only one-third of the cases are recognized early, and that 10 per cent involve the lung In the 16 cases studied by the author the abscess arose in the perinephric tissues, or perforated into the perirenal fat from the kidney in all but two, one of which proved to be an abscess of the appendix, and the other an abscess from a perforating carcinoma of the cecum One other case, not included in this series, was diagnosed as a perinephric abscess, but was found to be one of disseminated pyogenic destruction of the kidney, sometimes called "carbuncle" (It was not morphologically a carbuncle, but more strictly a diffuse cellulitis) The one outstanding feature, which should assist the diagnostician to distinguish true perinephric abscess from all the other conditions mentioned here, is its slow and insidious onset

Fifteen cases are herewith very briefly reported, in which the diagnosis of perinephric abscess was made, and was, so far as could be determined, correct in 14 instances, one case is included in which the diagnosis was that of an abscess of the appendix, which, however, proved to be a perinephric abscess Where the lapse of time from an original infection elsewhere could be determined, it averaged a few weeks In eight cases such a focus could be discovered, as follows

Upper respiratory tract	3
Pelvis or appendix	3
Pustules	2

All recovered except one, an instance of mistaken diagnosis, the true condition being an abscess resulting from a perforated carcinoma of the cecum, of which the patient died

ABBREVIATED CASE REPORTS

Case 1—Male, age 17 Onset several weeks after apparently clean appendectomy Discharged well following drainage

PERINEPHRIC ABSCESS

Case 2—Female, age 23 Onset several weeks after pelvic inflammatory disease Discharged relieved two weeks after drainage

Case 3—Female, age 30 Onset three weeks after tonsillectomy Diagnosis clear, though the process subsided without operation

Case 4—Age 35 No discoverable primary focus Satisfactory cure following drainage

Case 5—Female, age 25 Onset several weeks after childbirth Diagnosis clear, though the process subsided without operation

Case 6—Male, age 17 Onset five weeks after infection of heel Discharged well four weeks after drainage

Case 7—Male, age 28 Only discoverable primary focus was a pustule on the face, five weeks before entry Discharged relieved 18 days after drainage

Case 8—Male, age 23 Inflammatory tumor of right flank, of many weeks' duration, thought to be an old abscess of the appendix Celiotomy revealed a normal appendix, with a retroperitoneal inflammatory mass lying below the lower pole of the right kidney This subsided without direct drainage

Case 9—Female, age 46 No primary focus Operation revealed abscess in perirenal fat anterior to kidney Discharged relieved in four weeks

Case 10—Female, age 53 Symptoms had persisted five weeks No primary focus Perinephric abscess was suspected, but the lesion was so high that surgical approach was made transpleurally, resecting the tenth rib in back The pus was located in the perirenal fat just below the liver The patient was discharged on the eighteenth day after operation

Case 11—Male, age 24 This case was unusual because of short duration of symptoms (ten days), with acute pain for four days before entry Operation revealed an abscess at the upper pole of the right kidney, partly within and partly without the capsule Patient discharged relieved, after three and one-half weeks Stretching of the capsule by a subcapsular abscess may have accounted for the pain

Case 12—Female, age 49 Onset two weeks after acute mastoiditis Operation revealed a perinephric abscess which had apparently broken out from the cortex of the lower pole This case, like the preceding, was characterized by having severe pain The patient was discharged relieved seven weeks after operation

Case 13—Male, age 16 A feebleminded boy No primary focus discovered The first unusual signs occurred six weeks before entry, and consisted of abnormal posture with flexion of the left hip Drainage of a left perinephric abscess was successful, and the patient was discharged at the end of two and one-half weeks

Case 14—Male, age 35 After ten days of vague abdominal distress a deep mass was detected in the right flank, between the costal margin and the iliac crest This was diagnosed perinephric abscess, but operation proved it to be an abscess of the appendix

Case 15—Female, age 35 Duration of symptoms several weeks One year previous to entry there had been a nephrolithotomy for calculi A huge abscess gradually developed after the patient had had ten months of apparent health Drainage was successful, and the patient was discharged two weeks after operation

Case 16—Female, age 70 A large mass, of several weeks' duration, was detected in the right flank Diagnosis was made of perinephric abscess Operation revealed a perforated carcinoma of the cecum The patient died of this several months after operation

Once the diagnosis has been made the treatment is simple, and consists of exploration and drainage through an incision parallel to and below the twelfth rib If, in addition to the discovery of the perinephric abscess one suspects extensive kidney drainage, treatment of the latter should be postponed to a future period

CONCLUSIONS

(1) Perinephric abscess is characterized by slow onset and late development of local signs and symptoms. Sharp pain and short duration suggest development within the kidney capsule and later perforation into the perirenal fat.

(2) Perinephric abscess should be sought for in all cases of long, unexplained fever. Roentgenologic examination should be made, and, when possible, bacteriologic study of a centrifuged specimen of urine.

(3) Immediate operation should consist of simple exploration and drainage.

REFERENCES

- ¹ Baum. Zur Fruhdiagnose der paranephritischer Eiterung und des Nieren abszesses. Zentralbl f Chir, 38, 956, 1916
- ² Bugbee, H G. Perinephritic Abscess. Am Jour Surg, 26, 255, November, 1934
- ³ Cabot. Case 21272. Perinephritic Abscess. New England Jour Med, 213, 29, July 4, 1935
- ⁴ Cabot, H. Blood-stream Infections of the Kidney. Brit Jour Urol, 8, 233, September, 1936
- ⁵ Christopher, F. A Text-book of Surgery. W B Saunders Co. 1936, p 1432
- ⁶ Counsellor, V S, and Emmett, J L. Perinephritic Abscess. Hydronephrosis with Spontaneous Rupture and Perinephritic Haematoma Simulating Abscess. Proc Staff Meetings, Mayo Clinic, 11, 44, January, 1936
- ⁷ Convelaire, R. Peritonitis of Pyelorenal Origin. Jour de chir, 47, 392, March, 1936
- ⁸ Cunningham, D J. Text-book of Anatomy. Wm Wood & Co, N Y
- ⁹ Cutler, C W, Jr. Anterior Perinephritic Abscess. Abdominal and Thoracic Complications. ANNALS OF SURGERY, 102, 478, September, 1935
- ¹⁰ Deane, E H W. Empyema Necessitatis Simulating Perinephritic Abscess and Cured by Aspiration. Lancet, 1, 987, April 27, 1935
- ¹¹ Douglass, R J. Abscess of the Perinephrium. Urol and Cutan Rev, 39, 698, October, 1935
- ¹² Duff, J. Perinephritic Abscess, Diagnosis and Treatment. Urol and Cutan Rev, 40, 86, February, 1936
- ¹³ Ewell, G H. Metastatic Infections of the Genito-urinary Tract. Wisconsin Med Jour, 35, 91, February, 1936
- ¹⁴ Nesbit, R M, and Keene, C H. Perinephritic Abscess with Bronchial Fistula. Univ Hosp Bulletin, Ann Arbor, 2, 19, April, 1936
- ¹⁵ Richardson, E P. Perinephritic Abscess. Surg, Gynec, and Obstet, 21, 1, July, 1915
- ¹⁶ Rusche, C F, and Bacon, S K. Unusual Conditions Simulating Perinephritic Abscess, with Report of 10 Cases. Jour Urol, 34, 504, December, 1935
- ¹⁷ Schonfeld, W A. Renal Calculi in Infants Complicated by Abscess and Subarachnoid Haemorrhage. Am Jour Dis Child, 50, 686, September, 1935
- ¹⁸ Shane, J H, and Harris, M. Roentgenologic Diagnosis of Perinephritic Abscess. Jour Urol, 32, 19, July, 1934
- ¹⁹ Swan, C S. Perinephric Abscess. New England Jour Med, 209, 180, July 27, 1933
- ²⁰ Walters, W. Acute Obstructing and Inflammatory Lesions of the Kidneys and the Ureters. ANNALS OF SURGERY, 98, 785, October, 1933
- ²¹ McVay, J R. Perinephritic Abscess, Diagnosis and Treatment. Jour Missouri Med Assn, 32, 10, January, 1935

POSTOPERATIVE USE OF INSULIN IN THE NONDIABETIC

WITH SPECIAL REFERENCE TO WOUND HEALING

FRASER B GURD, M D , F R C S (CAN)

MONTREAL, CANADA

FROM THE MONTREAL GENERAL HOSPITAL MONTREAL CANADA

LONG before the work of the Toronto group—Banting, Best, McLeod, Collip and their coworkers—was successful in isolating insulin, in 1921, it was recognized by surgeons generally that the diabetic patient was singularly susceptible to the untoward effects of infective processes, and that frequently operative wounds in such cases did not heal promptly. Following the isolation of insulin, it was soon noted that, in the diabetic, not only might other signs and symptoms of the diabetic processes be controlled, and the life expectancy of the patient prolonged, but that surgical procedures were rendered possible on such patients with comparative safety, both as regards life and wound healing. The employment, therefore, of insulin in the treatment of diabetics in whom operative procedures are deemed either wise or necessary has become a routine procedure. Foster,¹ soon after insulin was introduced, pointed out that the mortality rate from infection in the diabetic had been reduced by means of insulin from 40 to 12 per cent.

In this connection, Rabinowitch,² in 1932, published a study of a series of 250 consecutive cases of gallbladder disease operated upon in the Montreal General Hospital, of whom 50 were diabetics. This analysis proved that in this limited number of cases it was possible to operate upon the diabetic without any greater mortality rate than was found among the nondiabetics. As a matter of fact, the death rate among the diabetics was 4 per cent, whereas in the controlled nondiabetic group, it was 5.5 per cent.

That, in addition to the diabetic, there are a large number of patients who exhibit either very slight or moderate disturbances of carbohydrate metabolism and in whom, furthermore, surgical interference may be more safely and more adequately carried out if insulin is administered, is apparently not generally appreciated by surgeons. The purpose of this contribution is, therefore, to support the thesis that wound healing in both primarily infected and clean wounds may be expected to progress more quickly and favorably if, during the postoperative period, insulin is administered up to safe limits of tolerance.

Although the writer is of the opinion that tissue injury, whether due to accidental or operative trauma, is likely to disturb carbohydrate utilization, proof of this point of view will not be offered at this time. Our observations would seem to prove that not only is carbohydrate tolerance likely to be disturbed by infective processes, but that the very fact of tissue trauma as the result of accident or operation is similarly likely to interfere with carbohydrate utilization, with consequent hyperglycemia of a greater or less degree and, also, we believe, concomitant interference with, or delay in, wound healing.

That the postoperative administration of insulin may have concomitant useful purposes other than those affecting the ability of the tissues to overcome infection and to hasten wound healing would seem probable. In 1923, Thalhimer³ reported three cases, with an analysis of the effect of the injection of glucose solution plus insulin in postoperative vomiting and ketosis. These observations seemed to prove that the untoward symptoms cleared up rapidly—much more rapidly than had been accomplished with the employment of glucose alone. Our own experience would seem to indicate that this is true.

In 1931, and again in 1933, Gage, Ochsner and Cutting⁴ presented careful experimental evidence which seems to prove that whereas dextrose alone caused an inhibition of intestinal activity both in the normal and in the obstructed intestine, dextrose and insulin combined resulted in an increase in activity. In other words, that dextrose solution exerts an inhibiting effect on the normal and obstructed intestine which can be largely obviated by the use of insulin. They make the suggestion that clinically dextrose alone be used cautiously and that it be combined with insulin in order to minimize the inhibiting effect it may have on the intestines. For many years and prior to the publication of Gage, Ochsner and Cutting's article, we have been accustomed to add insulin (unmodified) to all solutions of glucose-saline given intravenously. Although the usefulness of this procedure is difficult to prove statistically, we have been impressed by the greater feeling of well being experienced by the patients in whom this technic has been used. For this purpose we have added insulin at the rate of one unit, to from 2 to 5 Gm. of dextrose, being guided in this respect by the blood sugar content.

Williams and Dick,⁵ in 1932, after an adequate résumé of the literature upon the subject, starting from Hibbard's article, in 1899, report their own observations on a large series of cases of infectious disease and experimental infection in animals, with special reference to the development of glycosuria under these conditions. Glycosuria, they note, occurred in 41 per cent of patients with infectious disease when given a sufficient amount of dextrose. Such glycosuria was accompanied by lower carbohydrate tolerance, in both men and animals, under conditions of infection. They also noted that the administration of insulin improves dextrose tolerance in the presence of infection. They expressed the opinion that their work suggested that in infectious disease there is often an injury to the islets of Langerhans with lessened production of insulin.

Although not generally appreciated, it has been recognized that, as Rabinowitch⁶ has pointed out, it is a fact that in the presence of infection not only may the supply of insulin produced in the body be reduced but, also, that the insulin which is administered hypodermically may be affected in its usefulness. In postoperative cases showing but slight hyperglycemia, it may also be found that larger doses of insulin are tolerated and may, in fact, be more profitably administered than would be indicated in cases of mild or potential diabetes not subjected to infection or trauma.

Since 1924, at the Montreal General Hospital, stimulated by the co-

operation and interest of Dr. I. M. Rabinowitch, director of the Department of Biochemistry and Metabolism, several members of our staff have become increasingly interested in the effect of disturbed sugar metabolism in non-diabetics, especially with reference to wound healing.

In 1924, Dr. A. T. Bazin's attention was drawn to the following case which had previously been reported by him.⁷ Briefly, the essential features of it were that a woman, age 47, was admitted October 14, 1924. In August she had suffered a slight abrasion over the dorsum of the right foot. This became infected, the skin sloughed over an area of about four by five inches, and a Thiersch graft was employed to cover the granulating area without any result other than that the surface of the thigh from which the graft was removed also became an ulcer. Except for the fact that the patient was somewhat overweight, all general and special examinations were negative. All forms of treatment were employed, some of which seemed to result in improvement for a few weeks, but all without ultimate avail, the ulcers remaining about the same size.

Finally, Doctor Bazin states, on January 13, two months after admission, an examination of the blood (fasting) showed a blood sugar of 0.161 per cent. With regulation of the diet this promptly dropped to normal (0.08 per cent), the ulcers healed, and the patient was discharged February 2, 1925, only 20 days after discovery and correction of the real cause of the delayed healing.

Rabinowitch,⁸ in referring to this case, points out that neither the history, signs nor symptoms suggested diabetes, unless the slow healing of the wound be considered as a sign. At no time was there any glycosuria. The same patient was admitted in December, 1931. There was again no reason to suspect diabetes. Fasting blood sugar was found to be 0.116 per cent and the plasma cholesterol was 0.187 per cent. The urine was free from sugar and acetone bodies. There was, in fact, no fundamental disturbance of carbohydrate metabolism, in other words, the patient was not diabetic. First proof of this fact was supplied by the appended blood sugar time curve.

BLOOD SUGAR TIME CURVE, FOLLOWING ADMINISTRATION OF
100 GM. OF DEXTROSE

Time	Blood Sugar
Fasting state	0.114 per cent
30 minutes after dextrose	0.126 per cent
60 minutes after dextrose	0.116 per cent
120 minutes after dextrose	0.111 per cent
150 minutes after dextrose	0.100 per cent

Here, therefore, is reported a case in an individual who shows no evidence whatever of abnormal carbohydrate metabolism, whose tissues, under the stimulus of a mild infective process, exhibited hyperglycemia, and in whom two wounds which had proved resistant to the repair process over a period of months promptly recovered when the blood sugar values were reduced to normal.

At the Montreal General Hospital, since about 1930, estimation of the

blood sugar has become a routine procedure in cases in which slow healing of wounds has been exhibited. On some of our services such examinations prior to operation have become a routine in all patients who are over age 40. In the cases in which wound healing seems to have been delayed, as well as, it may be added, in a large proportion of all persons admitted for surgical interference over age 40, a common finding is mild hyperglycemia, the blood sugars often range between 0.13 and 0.16 per cent, and in many others, although normal fasting values are discovered, the time curves show abnormalities. That these findings have not been accidental may be seen by repeated analyses of the blood from the same patients made at different intervals. These facts have already been reported by Rabinowitch.⁸ He supports the view that such figures are not accidental by the following observations:

Date	Blood Sugar Per Cent	Time Interval Between Tests Days
February 16	0.143	
17	0.139	1
19	0.131	2
22	0.137	3
29	0.140	7
March 7	0.149	7

During the past seven years many thousands of blood sugar time curves have been prepared by Rabinowitch and his staff. These studies have shown that many individuals whose fasting blood sugar values are within normal limits, *e g*, 0.08 to 0.12 per cent, nevertheless, show substantial proof of disturbed sugar metabolism. In connection with the recording of the blood sugar time curve, Rabinowitch and Bazin⁹ have previously discussed the essential details of carrying out the test and have, more especially, drawn attention to the importance of the "peak" and the "lag" as shown by the charted figures.

Following Rabinowitch's advice in the matter, a curve in our opinion is regarded as normal when

(1) The blood sugar in the fasting state (before glucose) is normal (0.08 to 0.12 per cent)

(2) After glucose, the maximum blood sugar ("peak") is not greater than 0.18 per cent

(3) The "peak" occurs at the 30 minute period

(4) The blood sugar is again normal, or below, at the 120 minute period, that is, two hours after the glucose is given

The following figures taken at random indicate the abnormalities under discussion

(1) Fasting	119 per cent	50 Gm dextrose	30 minutes—	200 per cent
			60 minutes—	250 per cent
			90 minutes—	166 per cent
			120 minutes—	131 per cent

(2) Fasting 095 per cent 50 Gm dextrose	30 minutes—	137 per cent
	60 minutes—	200 per cent
	90 minutes—	192 per cent
	120 minutes—	181 per cent
(3) Fasting 117 per cent 50 Gm dextrose	30 minutes—	149 per cent
	60 minutes—	227 per cent
	90 minutes—	122 per cent
	120 minutes—	089 per cent

In the opinion of some of us, perhaps the most impressive finding as the result of the enormous number of blood sugar time curves which have been carried out on our surgical patients has been that, whereas it is possible to estimate the degree of carbohydrate metabolism abnormality if fasting blood sugar figures are above normal, very little information is obtained if such figures are within normal limits, *e g*, 08 to 12 per cent. In such cases the accurate estimation of the blood sugar time curve—30, 60, 90 and 120 minutes following the ingestion of 50 Gm of glucose—may give information which is of the greatest value.

In this connection, even though the blood in the fasting state may show a normal sugar value and, at the end of 120 minutes will be shown to have returned again to normal, the repeated examinations made show both a "lag" and, also, an abnormally high "peak." Normally the highest figure is obtained at the end of 30 minutes. If the highest figure is obtained at the end of the 60 or 120 minute period, the "lag" is said to be present. The "peak," or highest figure, which in Rabinowitch's opinion should be less than 18 per cent, may be noted at the end of 30 or 60 minutes.

During recent years a sufficiently large number of cases, who demonstrated more or less marked disturbances of carbohydrate metabolism and who tolerated and were apparently benefited insofar as wound healing was concerned, have been reexamined later and normal blood sugar time curves established to prove that they were not diabetics.

ILLUSTRATIVE CASE REPORTS

Case 1—Hospital No 2626/36 W J E D, age 63, was operated upon, under spinal anesthesia, October 3, 1936, in order to drain a retroperitoneal abscess, lying behind the cecum, consequent upon a perforated retroperitoneal appendix. The abscess was about the size of a fist. The proximal half of the appendix was identified and removed, the distal half having been judged to have been gangrenous and to have been removed along with the purulent exudate. The abscess cavity was "bipped" and firmly packed with liquid paraffin "bipped" gauze¹⁰. The abdominal wound was "bipped" prior to opening the abscess. In addition, a large pack was inserted down to the right side of the pelvis.

Blood sugar examinations were made: October 2, 0140 per cent, October 5, 0122 per cent, October 10, 0104 per cent, October 19, 0103 per cent, and November 4, 0093 per cent.

Insulin was administered commencing October 3, five units every six hours. The remaining blood sugar estimations were carried out while insulin was being employed.

The patient received several intravenous glucose-saline 5 per cent, 750 cc infusions after October 4, to each of which ten units of insulin were added, in excess of the routine insulin which he was receiving.

Both packs were removed on the fourth day, and from this time on, patient's course

was afebrile, with one or two exceptions. He was discharged with the wound soundly healed November 7, *i.e.*, 35 days following operation. He was allowed up in a chair for 20 minutes October 18, 15 days after operation. No further insulin, or dietary control, has been employed since discharge from hospital. A fasting blood sugar examination made February 15, 1937, showed this figure to be 0.12 per cent.

It is, of course, impossible to make a positive statement as to what the course of events would have been had insulin not been administered, at the same time, the gravity of the patient's illness, coupled with his age, made it appear that a very serious outcome both as regards life and length of illness might have been expected. The wound as a whole healed kindly, without spreading inflammation, and the whole period of illness was, in our opinion, gratifyingly short. That the patient was not a diabetic is, I believe, proven by the data supplied.

Case 2—Hospital No 1513/36 W. P. E. D., age 34. Admitted June 1, 1936, 48 hours after a motor accident. He was found to be suffering from a fracture of both bones of the left leg, fracture of both femora, large depressed fracture of the left temporal region, multiple fractured ribs, on both sides, and injury to the left kidney. In addition, the left leg showed complete absence of popliteal and distal pulsation.

Following admission, fasting blood sugar records, June 4 and June 26, showed blood sugar to be 0.108 per cent. On June 29, the blood sugar time curve showed the figures to be 0.114, 0.149, 0.181, 0.200 and 0.181 per cent. Following this examination he was placed on five units of insulin every six hours. Fasting blood sugar examination July 6 showed it to be 0.137 per cent. The dose of insulin was then raised to 24 units a day—ten at 8 A.M. and five at 2 P.M., 8 P.M. and 2 A.M. While still receiving insulin, the following percentages were obtained: July 13, 0.111; July 20, 0.125; July 30, 0.112; August 26, 0.095; and October 10, 0.109 per cent.

On July 13, the insulin was reduced to five units every six hours, and on October 13, four days before discharge, it was reduced to five units every eight hours.

That the patient was not a diabetic is proven, I believe, by the fact that his early blood sugar examinations, after admission to hospital, were low. At no time during his stay in the hospital was sugar demonstrated in the urine, and, on January 20, 1937, the appended blood sugar time curve was obtained:

	Percentage Blood Sugar	Urine Sugar
During fasting state	0.090	0
30 min. after glucose	0.126	0
60 min. after glucose	0.133	0
120 min. after glucose	0.133	0
150 min. after glucose	0.120	0

Note: There is no evidence of diminished tolerance.
There is no evidence of delayed assimilation.
Given 50 Gm. glucose in 250 cc. water.
Nausea absent.
Vomiting absent.

His various injuries were treated serially. Immediately upon admission his condition was extremely grave and it looked as though an early exitus might be expected. With improvement in his general condition, with admin-

istration of intravenous glucose-saline to which insulin at the rate of one unit to five units of glucose was added, and blood transfusions, he developed symptoms of acute mania

June 10, operation was performed for relief of a large depressed fracture in the left temporal region, which extended down toward, and involved, the base of the skull

June 18, two Kirschner wires were inserted into the left lower extremity, under combined gas and spinal anesthesia (Prior to this time skin traction had been employed with the right limb in a Braun splint) One wire was placed through the middle of the left femur and one through the left os calcis The right limb was placed in a plaster-of-paris encasement

From the time of his admission his temperature ran an irregular course, ranging from normal to 101° F and, on two occasions, to 103° F

By July 13, the left leg, which had become gangrenous up to the middle, appeared to be responsible for the febrile condition The mental condition had cleared up rapidly following operation upon the skull

On July 13, union of the left femur seemed sufficiently strong to permit manipulation and amputation of the gangrenous leg and removal of the Kirschner wire from the femur Amputation was of the guillotine type On August 17, reamputation was performed and the stump partially closed Again, September 1, further attempt at closure of the stump wound was made

Immediately following a sugar tolerance test, June 29, an increase in insulin administration was made and the temperature, which for the previous three weeks had never been normal and which had ranged daily between 101° to 103° F, dropped, so that the maximum for the following four days was 99.2° F

About July 9, the temperature commenced to rise, reaching 101.2° F or thereabout, daily Amputation was performed July 13 and insulin again increased July 17, the temperature was 99° F at its highest, and remained so during the remainder of his stay in hospital

Although, of course, the statement is open to argument, there is no question in my mind that this patient would have died as the result of the infective process having its origin in the right leg, had it not been for the exhibition of relatively large doses of insulin The improvement in the man's general condition, and in the appearance of the limb, following the initial administration of insulin and its subsequent increase in quantity, was such as to make it difficult to avoid this conclusion

In a recent article by C V Ward,¹¹ in which an analysis of 400 cases, admitted for repair of a damaged birth canal in the Gynecologic Service* of the Montreal General Hospital, is made, the importance of disturbed sugar metabolism in the healing of wounds is well shown

Ward reports that, between 1929 and 1933, there were admitted for repair of the birth canal 400 cases In 257 of them, blood sugar estimations† were carried out and in 42 per cent of these cases (110) the fasting blood sugar was found to be above 0.120 per cent

All cases showing blood sugar above normal were prepared for operation by diet, or diet plus insulin That these procedures have proved to be of value is shown by the fact that in cases with normal blood sugar, 95 per cent resulted

* A D Campbell, M D, Director

† Blood sugar estimations routine in all public ward cases but not for private cases

in sound healing, whereas in the cases with elevated blood sugar, 94 per cent were followed by good operative results

Ward's series of cases shows that, in instances of elevated blood sugar, only 25 per cent, at any time, showed sugar in the urine. Of the total number of 400 cases, but 20, or 5 per cent, were judged to be diabetics. This, notwithstanding the fact that in 42 per cent, fasting blood sugar was found to be above normal, and in 67 cases, or 17 per cent, insulin was employed both before and after operation.

It would seem necessary in view of the wording of the title of this article to refer to the question, to what extent carbohydrate metabolism must be altered or interfered with in order that the individual should be classified as a diabetic. A. T. Bazin's first reported case was evidently not a diabetic, nevertheless, hyperglycemia was present during the inflammatory stage of her wounds and, although a tendency toward healing had been absent for a period of many months prior to a specific dietary control of the hyperglycemia, following the reduction of the blood sugar content to normal, healing promptly occurred. The two patients, Cases 1 and 2, whose histories are abstracted herewith, are clearly not diabetics. Scores of similar cases might be cited in which similar results have been obtained.

Although observation and study of many cases over a period of years and analyses of numerous blood sugar time curves have impressed us with the importance and usefulness of insulin administration in even the mildest grades of hyperglycemia in the promotion of wound healing, it must be borne in mind that insulin is a dangerous preparation and that it may cause death. Although we are convinced that in a very large proportion of persons suffering from infected wounds and trauma, more particularly in those over 40 years of age, wound healing can be expected to progress more favorably if insulin be administered up to the limit of tolerance, we wish to insist that the exhibition of insulin must be carried out only with the patient in a hospital and under careful observation both as to clinical state and blood sugar estimations. Although we believe that five units of the old insulin may safely be administered every eight hours in the presence of trauma, in practically all adults, more particularly over 40 years of age, we are convinced of the necessity for blood sugar studies both before and also, as a rule, after insulin has been administered. Furthermore, such cases must be observed closely for even mild symptoms of insulin shock.

Since the introduction of protamine zinc insulin, we have employed ten units of the new preparation given in the morning (at eight o'clock) instead of 15 units of the old insulin given in divided doses. We do not wish to suggest that ten units of protamine zinc insulin or 15 units in the 24 hours of the old insulin is always sufficient dosage in nondiabetic cases, we wish, however, to insist that such dosage should not be surpassed unless the most accurate chemical investigation of the patient's blood is possible.

The following memorandum is probably unnecessary but the matter is of such supreme importance that I believe it should be referred to here.

Since there are available on the market at the present time the two forms of insulin, it becomes imperative that in individual cases the form of insulin prescribed should be made clear to attending staff, nurses, interns, *etc*, and to the dispenser, since it is possible to safely and properly administer a sufficient number of insulin units in the protamine zinc form in one dose which might prove fatal if the old unmodified insulin, all of which becomes potent soon after its introduction into the body, were employed in similar dosage.

We are not prepared at the present time to make a positive statement with reference to the relative value with regard to wound healing of the old (unmodified) and the new (protamine zinc protected) insulin. It is, however, probable that, in certain cases at least, the best results are obtained by the use of both preparations at suitable times and in proper dosage.

Since, when insulin is added to an intravenous solution of glucose it is hoped that it will immediately assist the tissues in utilization of the injected dextrose, it would seem advisable, indeed necessary, to use for this purpose the original insulin preparation and not the protamine zinc insulin.

REFERENCES

- ¹ Foster, N. B. Surgical Aspects of Diabetes, J A M A, 84, 572, 1925
- ² Rabinowitch, I. M. On the Mortality Resulting from Surgical Treatment of Chronic Gall-Bladder Disease in Diabetes Mellitus. ANNALS OF SURGERY, 70, July, 1932
- ³ Thalhimer, W. Insulin Treatment of Postoperative (Nondiabetic) Acidosis. J A M A, 81, 383, August 4, 1923
- ⁴ Gage, I. M., Ochsner, Alton, and Cutting, R. A. Effect of Insulin and Dextrose on the Normal and on the Obstructed Intestine. Arch Surg, 24, 658, 1933
- ⁵ Williams, J. L., and Dick, G. P. Decreased Dextrose Tolerance in Autoinfectious Diseases. Arch Int Med, 50, 801, 1932
- ⁶ Rabinowitch, I. M. The Influence of Infection upon the Reaction of the Diabetic to Insulin Treatment. Canad M A J, 26, 551, 1932
- ⁷ Bazin, A. T. Surgical Problems Presented by the Diabetic. Canad M A J, 23, 146, 1930
- ⁸ Rabinowitch, I. M. Simultaneous Respiratory Exchange and Blood Sugar Time Curves. Arch Surg, 26, 696, 1933
- ⁹ Rabinowitch, I. M., and Bazin, A. T. Application and Interpretation of Blood Sugar Time Curves in the Diagnosis and Treatment of Surgical Infections of the Gall-Bladder and Biliary Passages. ANNALS OF SURGERY, 354, September, 1931
- ¹⁰ Gurd, Fraser B. The Operative Treatment of Acute Appendicitis with Perforation. Canad M A J, 27, 360, 1932, A Specific Technique for the Treatment of Acute Appendicitis. Am Jour Surg, 17, No 1, 52, 1932
- ¹¹ Ward, C. V. The Value of Blood Sugar Studies in the Treatment of Damage to the Birth Canal. Canad M A J, 35, 298, 1936

SKELETAL TRACTION IN THE TREATMENT OF FRACTURES AND DISLOCATIONS OF THE CERVICAL SPINE

WILLIAM E GALLIE, M D

TORONTO, CANADA

REVIVAL of our interest in fractures and dislocations of the cervical spine dates from the paper of Davis, in which he showed that crush-fractures of the dorsal and lumbar vertebrae, unaccompanied by serious injury to the spinal cord, were best treated by reducing the impaction and immobilizing in hyperextension until healing occurred. Fractures and dislocations of the cervical vertebrae, however, differ from the others in that the manipulation required is attended by much greater risk of injury to the cord. Many writers refer to the ease with which a fracture of the odontoid or a dislocation of the articular facets in the midcervical region can be manipulated into place, but I happen to have seen one that did not result so well, which left such a deep impression on my memory that I look on the ordinary manipulations that are usually recommended as quite unjustifiable. The risk of increasing the damage that may have already been done is so great that extraordinary precautions, it seems to me, should be taken to prevent it.

It would seem that steady traction applied to the skull would be the safest means of reducing the displacement. Unfortunately the ordinary method of applying such traction, by means of the leather halter, is ineffective and most uncomfortable. Heavy traction applied for any length of time causes pressure sores on the chin and occiput. These difficulties were overcome by the suggestion of my colleagues, R M Janes and K G McKenzie, that traction might be applied directly to the skull by ice tongs. Since the successful employment of this method on the first case, some five years ago, every such case admitted to hospital has been treated similarly.

Reference to the literature will show that skeletal traction for fractures and dislocations of the cervical spine has been advocated by others. Crutchfield recommends it and advises the use of special tongs which are narrower than the patient's head and which are applied by inserting the points into holes drilled in the upper part of the parietal bones. Turner and Cone apply the traction by means of a wire passed through burr holes in the skull. Both these methods have advantages where it is intended to leave the patient for any length of time with the traction applied, as they make it possible for him to roll on his side without the head tongs coming in contact with the bed. As it is not our plan, however, to leave the traction applied for any longer than is necessary to overcome the displacement, we have found it convenient to continue to use the simple ice tongs without modification, except to make them wide enough in the jaw to grasp the head at its widest part and to provide a lock which will prevent opening or further closing when they have been applied.

The application of the tongs is simplicity itself. Under local or intra-tracheal anesthesia, two tiny skin incisions are made, one above each ear, just below the most prominent part of the parietal bone. The points of the tongs are then introduced into these incisions and pressed firmly against the skull and driven about one-eighth of an inch into the bone by a sharp blow with a hammer. The tongs are then locked and the traction applied. I have never seen them slip out of place either as the result of heavy or prolonged traction or from the accompanying manipulations.

At first it was our practice to put the patient to bed with the neck hyper-extended over the end of a mattress and to keep the traction on continuously



FIG 1.—Skeleton placed on a Hawley table which has been equipped with a special apparatus to allow the application of a plaster jacket with the ice tong traction applied. The patient's trunk and head may be raised and lowered at will so as to correct displacements and to disengage dislocated articular facets.

for several days. While the patients made no objection to this and never complained of pain or discomfort because of the points of the tongs in the skull, nevertheless, we have abandoned it because in two cases a transient paresis of the deltoid, spinati, biceps and triceps appeared, indicating compression or stretching of the fifth cervical nerve. For this plan we have substituted one in which the heavy traction is applied only until the displacement is reduced, either as the result of the traction itself or of the combination of traction and manipulation or of traction and open operation. A plaster jacket incorporating the trunk and head is applied and allowed to dry before the tongs are removed (Figs 1 and 2).

The importance of immobilizing the head after reduction of the displacement cannot be overemphasized, as there is a strong tendency in many cases for the displacement to recur. This is particularly so where there has been a

crush-fracture of one of the bodies or a combination of a crush-fracture with a dislocation forward of the vertebra above. Textbooks recommend Thomas collars, molded leather splints, and jury masts with a halter, but these devices in my hands have proved worthless. The only splint that can be relied upon to prevent the recollapse of a crush-fracture of the body or a recurrence of a forward dislocation of one vertebra on the other is the plaster of paris minerva or head-jacket. This must extend down to incorporate the pelvis, as a shorter jacket does not immobilize the neck sufficiently and is quite likely to allow a recurrence of the forward displacement.

The central idea in the technic is that the displacement shall be reduced

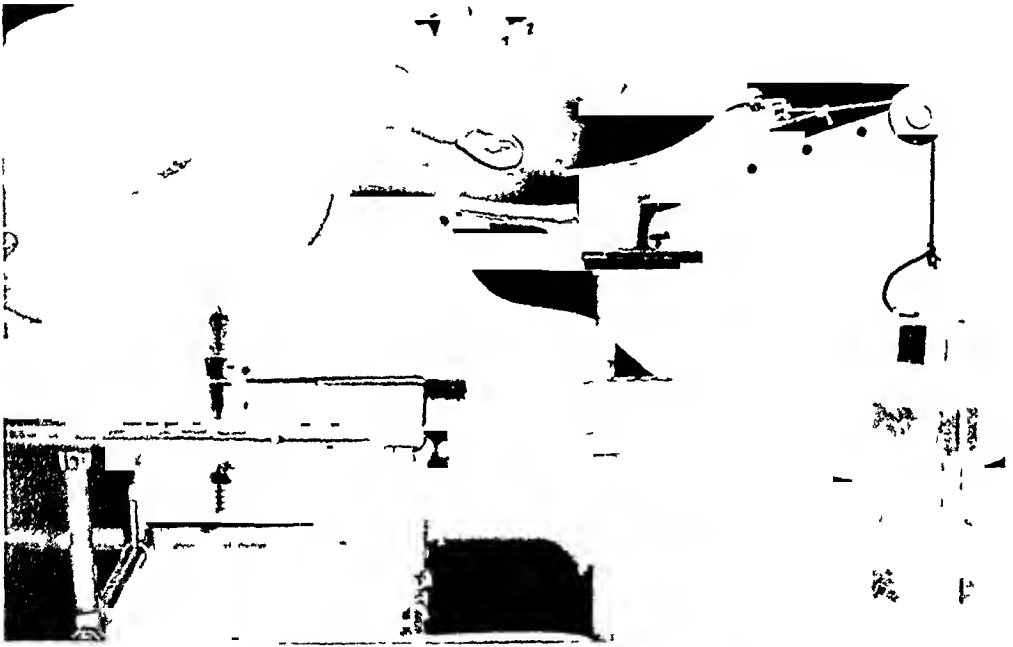


FIG 2—Photograph of a patient the roentgenograms of whose spine are shown in Figs 3 and 4, under anesthesia and with 30 pounds traction applied

with the minimum of risk of causing further damage to the cord. After the roentgenologic examination has shown the nature of the injury, the tongs are at once inserted and traction applied. The patient is then placed on a special apparatus which enables one to place the head and the segments of the cervical spine which are above the injury in the correct relation to those below and to maintain strong traction during the application of the jacket. From 20 to 30 pounds traction is applied for 10 or 15 minutes and then another roentgenogram is made. When the correction is complete the plaster is proceeded with, and as soon as it is set the tongs are removed (Figs 3 and 4).

This plan works admirably in simple crush-fractures and in moderately severe dislocations. It may fail, however, in cases in which the upper articular facets are locked in front of the lower ones—particularly where the dis-

placement has been present for some time. In recent cases there is no objection to adding gentle manipulation to the traction, but in those instances in which the displacement has been present for several weeks, manipulation is not likely to be successful and if persisted in is altogether too dangerous. In these cases the articular facets should be exposed through a dorsal incision and gently levered into correct relationship to one another. With the facets exposed, I have watched the effects of the manipulation of the head and in no case have I seen reduction accomplished by this method alone. Either the facets had to be levered into place or a portion of the superior facet of the lower vertebra had to be removed before replacement occurred.



FIG 3—Roentgenogram of patient who had sustained a slight crush fracture of the sixth cervical vertebra, and a gross forward dislocation of the fifth on the sixth cervical vertebra.



FIG 4—Roentgenogram of the same patient as shown in Fig 3 15 minutes after the application of the ice tongs traction.

The necessity for an open operation in these cases of forward dislocation in the cervical spine is less to be regretted when one remembers the marked tendency they have to recur, even after prolonged immobilization. It gives one an opportunity to fuse the articular facets by removing the articular cartilage and placing chips and slivers of bone around them after the manner of Hibbs. A successful fusion of the articular facets and laminae prevents all further forward slipping while causing no noticeable interference with the movements of the head and neck. Our experience has convinced us that one can foretell from the roentgenograms which cases are likely to have a tendency to recurrence after the removal of the plaster encasement and so save time by doing the fusion operation at once. One can do it either after the plaster bandage has been applied, through a large window, or, better still, it can be done with the ice tongs in action and the plaster applied afterwards. Very

satisfactory temporary fixation is provided by fastening neighboring spines together with steel wire

Our experience has now extended over four years and has included all varieties of fractures and dislocations of the cervical spine. The chief points we have learned are these:

(1) Skeletal traction applied to the skull is a safe and effective way of reducing the various displacements if employed soon after the injury.

(2) If reduction is delayed, however, for two or three weeks or more it will be necessary to expose the articular facets in order that the replacement may be accomplished with safety.

(3) In cases that have been reduced early and held effectively in a plaster encasement, the tendency to recurrence is slight, but in those that require operation, a fusion should be performed, as recurrence of the displacement is almost sure to take place.

DISCUSSION—DR. WILLIAM DARRACH (New York): I should like to speak about some of the milder varieties of the cervical injuries. Unfortunately for us, we have not had much experience with the more severe ones because if there are any associated cord lesions, they go to the Neurologic Institute, but we have had a number of cases of what we call unilateral subluxation of the cervical vertebra.

My attention was first called to this by a man who came to the College of Physicians and Surgeons, Columbia University, because he was not satisfied with his preliminary education in the school of osteopathy. He took a full course at medical school, and turned out to be one of our best graduates in a number of years. A few years after he got started, I referred a patient to him who came in to me with what I called an acute torticollis. He called me up the next day and thanked me for referring the subluxation to him, which he had reduced, with immediate relief, and hoped I would send him some more.

That was my first experience. In the last nine years we have had over 130 unilateral subluxations of the cervical vertebra. They are a most interesting group. The usual story is that they are walking down the corridor and somebody shouts to them, and they suddenly turn their head, and it stays there, or it may occur in getting out of bed, or upon sneezing, or coughing, or any sudden twist. It can be demonstrated upon roentgenologic examination. One usually requires stereoscopic pictures taken on both sides, but it is perfectly evident in the large majority of these cases that one of the articular facets has slid and been caught at least a half and sometimes three-quarters of the extent. Occasionally they will slide off and become the more serious type that Doctor Gallie has spoken of, with a locking. The milder cases will practically always reduce if they are given two forms of treatment, one rest, and the other mild traction. The form of traction which we have used, and which has been satisfactory in most of the cases, is simply a gravity pull obtained by putting the patient flat on the back on an air mattress with the head hyperextended, as described by Byron Stookey, sometimes with a little additional pull of two or three pounds. It usually reduces the displacement within 48 hours, occasionally 24 hours. At the end of that time they are simply immobilized with a plaster collar.

One of our cases had a recurrence because the plaster collar we put on proved to be uncomfortable to the lady, who wanted to go to a dance that night. She got her boy friend to cut it off. In the middle of the dance the

subluxation recurred and she came back for another collar. We have had no experience with the skeletal traction.

I saw a case Doctor Gallie demonstrated in Toronto, and I was impressed with the peace and happiness the man seemed to show, but I always wondered how many times the tongs pulled out. I am delighted to hear that they have not pulled out. I should like to ask Doctor Gallie how long he leaves the tongs on, that is, what he thinks is a safe length of time to leave them on, because I firmly believe that steady pressure on bone sooner or later will cause necrosis and slipping.

Everything I have said is based on the work of Dr Barbara Stimson, of our staff, who reported her observations in the *J A M A*, 104, 1578-1579, May 4, 1935, and in *Surg, Gynec, and Obstet*, 58, 1007-1017, June, 1934.

DR WILLIAM J MIXTER (Boston) I feel that Doctor Gallie's paper is a very timely one. I think that the modern methods of traction combined with fusion in these lesions of the cervical spine and elimination of laminectomy are a definite step in advance, and as a neurologic surgeon, I should welcome these suggestions.

DR CHARLES C LUND (Boston) I am rising just as a patient who has had a broken neck. In 1925, I was in an automobile accident, and I had my coronoid process cracked, but not displaced. I can still remember a good many of the sensations during the first few hours and days of that experience. The fracture of the coronoid is a little difficult to demonstrate roentgenographically, and was not demonstrated in my case during the first few days. During that time, attempted traction was made with a cardboard Thomas card, which gave some relief, but really not very much.

At the end of about a week, the diagnosis was definitely arrived at, and a real fixation with a molded leather apparatus of about the same size as the plaster encasement shown by Doctor Gallie was applied, and from then on I was entirely comfortable. I have a suspicion that if skeletal traction had been used during the time, before the final diagnosis was made, that I would have been a lot more comfortable, even if it would not have made any difference in the result.

DR FRASER B GURD (Montreal, Canada) During three years' membership in this organization, I have been impressed, as Doctor Gallie has suggested, with the fact that although to my knowledge a number of the Fellows were experts in the treatment of fractures and dislocations, such topics had not been presented for consideration before this body. I, therefore, agree with Doctor Gallie in his preliminary remarks.

I have felt that perhaps it is in order to draw attention to another feature of technic in the treatment of these fracture-dislocations of the spine, particularly of the first and second laminae, which has been used, as most of you, I presume, know, in Montreal having been, in the first place, suggested by Cone and Turner, at the Royal Victoria Hospital, and used at the Montreal General by Elvidge and Nutter, namely, the grafting of the skull to the upper cervical spine by means of grafts from the iliac bone. This technic used in connection with skeletal traction as employed by them, with two bore holes on either side of the skull, has proved, I believe, perfectly satisfactory. The patients are comfortable where that method has been employed. Union of the base of the skull with the upper cervical spine is effected, so that risk of redisplacement of the skull upon the first or second vertebral bodies is rendered impossible.

DR WALTER E LEE (Philadelphia) I had the privilege, some three years ago, of seeing this apparatus, and its method of extension, applied at a clinic given by Doctor Gallie in Toronto. The comfort of the patient, in spite of the fact that he had been in extension for nearly 48 hours, was surprising. There was a complete reduction. The question that arose among the group of visitors was the possibility of necrosis of the bone or meningitis. I have discussed this with Doctor Gallie recently, and he tells me no such complication has developed in any of his cases.

DR FREDERIC J COTTON (Boston) I would like to ask Doctor Gallie if he has ever tried a procedure I did once some years ago, namely, the lacing of wire about the spinous processes above and below the level of the damage, going in and out about the spines in front of the ligamentum nuchae. It worked out extraordinarily well in one case and might be worth doing again.

DR WILLIAM E GALLIE (Toronto, Canada) closing. I am very pleased indeed with the amount of discussion this little clinical paper has aroused. In reply to Doctor Cotton, I would say that I have had experiences similar to his with the use of wire and that I think it is an excellent method, but in the more serious cases, particularly where there is a crush of the anterior edge of the vertebra below, it seems to me that a fusion should be performed as well, as by this means a more permanent result will be obtained.

To Doctor Heuer, I would say that we have no special roentgenologic equipment but use a simple portable apparatus which takes the lateral and vertical positions.

To Doctor Darrach I would say that the longest time we ever left the tongs in place was a month. As I said in the paper, on two occasions heavy traction applied for over 24 hours produced weakness of the shoulder girdle so that we now try to complete the reduction and get rid of the traction within two or three hours. In one case, however, we had it on for a month without any ill effect whatsoever.

I should like to take this occasion to thank Doctor Darrach for his remarks. Many years ago, when I was very young, he came to Toronto to address the Medical Society and I led an attack on his paper. Since then he has never missed an opportunity to heap coals of fire upon my head by the nice things he has had to say.

RUPTURE OF THE LUMBAR INTERVERTEBRAL DISK

AN ETIOLOGIC FACTOR FOR SO-CALLED "SCIATIC" PAIN

WILLIAM JASON MIXTER, M D

BOSTON, MASS

FROM THE SURGICAL SERVICES OF THE MASSACHUSETTS GENERAL HOSPITAL BOSTON, MASS

SCIATICA is a common complaint. We believe we can show that an unknown but probably a small percentage of cases of intractable "sciatic" pain are caused by rupture into the spinal canal of a lumbar intervertebral disk, that the lesion can be accurately demonstrated and that operative treatment will effect a cure.

In preliminary communications^{1, 2} we have traced the earlier literature concerning rupture of the intervertebral disk. Notable among these contributions are those of Goldthwait,³ Middleton and Teacher,⁴ Dandy,⁵ and Schmorl.⁶ We linked with these the reports of so-called enchondroma of the intervertebral disk especially emphasized by Elsberg⁷ and Stookey⁸ and reported Barr's¹ recognition of the fact that these two lesions usually were one and the same, and not separate entities. True enchondroma of the spine does occur, but it is rare.

Since our last observations,² certain other reports have been published relative to this condition, notably those by Hampton and Robinson⁹ concerning the roentgenologic findings in these cases, that by Love,¹⁰ from The Mayo Clinic, and that by Barr.¹¹

While most of the cases reported here have been operated upon by me, I wish to thank Dr. John S. Hodgson and Dr. James C. White for allowing me to include their cases. I also wish to thank the neurologic, orthopedic and roentgenologic departments. Without their cooperation this work could not have been accomplished.

We have been particularly interested in those cases in which one or the other of the two lower lumbar disks were affected. They are by far the most common and we believe that many have been overlooked in the past.

Extrusion of a small disk fragment into the spinal canal usually causes none of the signs that we associate with lesions of the cauda equina. In common with several well-known diseases such as lumbosacral strain, sacroiliac strain, *etc.*, this condition is characterized chiefly by pain. This pain is of the type referred to for many years as sciatica. If, as occasionally happens, the extruded disk fragment is large, the signs are similar to those found in cases of tumor of the cauda equina.

About 60 per cent of these cases will give a history of trauma at, or shortly before, the onset. The one outstanding feature is pain, starting in the back, streaming down the thigh and the outer side of the leg to the ankle. The pain is severe, lancinating in character, is brought on by bending or lifting and is usually lessened by lying down and sometimes by strapping. The pain

comes in attacks and there may be long remissions. There is limitation of motion in and flattening of the lower back. Frequently there is a list to the side of the lesion. Ability to raise the leg in extension is limited. This is the one positive, objective sign present in all cases but is of little diagnostic significance because of the frequency with which it occurs from other causes. In some cases raising the good leg will cause pain in the bad one. Neurologic signs are few. The one that we have come to expect is absence or diminution of the ankle jerk on the affected side. Even this sign is absent in at least 40 per cent of our cases. Roentgenologic examination of the lumbar spine occasionally shows narrowing of the intervertebral disk but this is not common enough to be of diagnostic significance. In those cases where there is gross compression of the cauda equina we find much more outspoken signs and symptoms but, as stated above, these are rare.

It is apparent that a diagnosis of ruptured disk cannot be made on such meager evidence, but such evidence is enough to arouse suspicion.

Unless conservative orthopedic treatment brings relief in a reasonable length of time, every case presenting this picture of intractable sciatic pain, splinting of the back and limited straight-leg raising should have a lumbar puncture performed. The needle is inserted into the fifth space or if this is impossible, into the fourth, and the first few drops of fluid withdrawn are set aside for determination of the total protein. The usual routine manometric and laboratory examinations are made but are usually uniformly negative. The one important test is the determination of the total protein in the first fluid withdrawn. This is important, as the fluid higher up in the lumbar portion of the spinal canal may show a normal protein content even if that low down is abnormal.

We may assume that a total protein content of 40 or 45 mg per cent is the upper limit of normal and that any figure above this level is highly suggestive of some pathologic condition. If this is the case, examination of the spinal canal with lipiodol is indicated. As 15 per cent of proven cases showed a total protein of below 40, the presence of a normal spinal fluid will not rule out ruptured disk. Lipiodol examination is indicated in cases with normal protein content before major orthopedic operations such as lumbosacral or sacro-iliac fusion are performed.

The final diagnosis of ruptured disk rests almost entirely on the roentgenologic examination following the injection of 5 cc of lipiodol into the lumbar portion of the spinal canal. It is not necessary to go into the technic of this examination. It has been well described by Hampton and Robinson.⁹ In order to obtain accurate information this technic must be carried out very carefully. It includes careful fluoroscopic examination on the tip table, the lipiodol being run up and down repeatedly in the spinal canal and spot plates taken when the defect is demonstrated.

We know that lipiodol seldom gives any lasting symptoms but it is never absorbed and therefore should not be employed unless the indications are clear.

I believe it should be reserved for those cases with an elevated total protein, those in which adequate and prolonged orthopedic treatment has been unsuccessful, and in which some other definite cause of sciatic pain cannot be found.

The causes of a total protein content above normal limits need further investigation. We have records of 21 unoperated cases that were subjected to lipiodol examination with negative findings. In four the total protein was below 40 and in 17 the elevated protein content has not been explained satisfactorily.

It is uncertain whether rupture of an intervertebral disk is entirely the result of injury or whether there may be an underlying weakness in the disk.

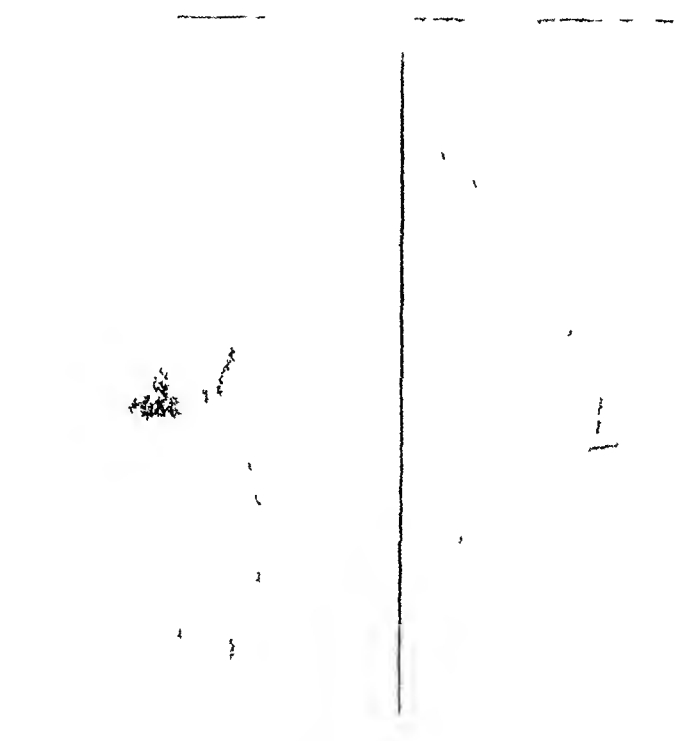


FIG 1—Rupture fourth lumbar disk. Large lateral defect in lipiodol column.

FIG 2—Rupture fourth lumbar disk. Moderate sized defect. (New England Jour Med, August 29, 1935)

itself. It is certain that we find this lesion in a few individuals who deny specifically ever having had any serious back injury.

The lesion commonly found at operation is a definite break in the annulus with protrusion into the spinal canal of a portion of the annulus accompanied by some of the nucleus pulposus (Fig 3). The extruded fragment usually lies anterior to the dura and the posterior longitudinal ligament and is compressed into a hemispherical mass by these structures. The fragment is irregular, appears to have been torn and frequently has no attachment to the rest of the disk. A definite opening in the annulus can be demonstrated leading down into the nucleus.

We believe that this lesion tends to permit increased mobility between the vertebral bodies. Therefore, we have planned our operative procedure with

this in mind It is unnecessary to perform an extensive laminectomy as long as the exposure is accurately planned Let us take, for example, a rupture of the fourth lumbar disk The laminae are exposed as usual, the spinous processes being preserved attached to the muscles on one side The lamina of the fourth lumbar vertebra on the affected side is resected The other side is left long, only a portion of it being removed The lower edge of the lamina above and the upper edge of the one below are removed care being taken not to remove the whole of either (Fig 4) It is now possible to palpate the spinal canal and the protruding fragment can be felt in most cases If the lesion is far out at the side of the disk or cannot be recognized the exposure

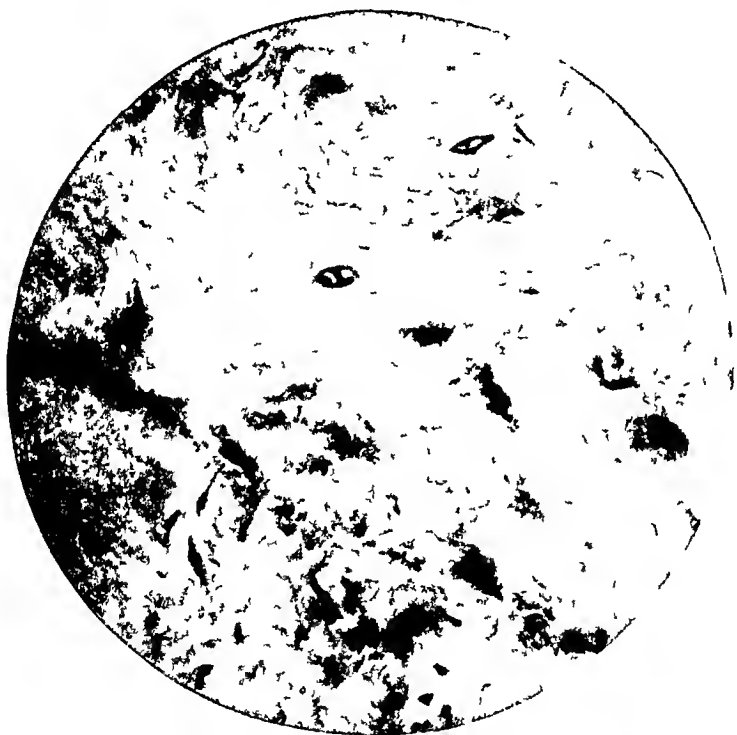


FIG 3—Photomicrograph from specimen obtained at operation. Material from annulus on the left, and from nucleus on the right

is widened by removing the articular process of the fourth entirely It will then be seen that the anterior border of the facet of the fifth and the ligamentum flavum overlies the fifth root sheath It is usually necessary to cut these two structures away even if the mass can be felt It probably is wise to do so anyway as the articular facet is the structure against which the fifth root is pressed by the disk fragment which lies in front of the root The lumbar portion of the cord is then drawn over toward the midline, either above or below the root sheath according to the position of the mass (Fig 5) This exposes the posterior longitudinal ligament which is incised and the fragment removed (Fig 6) It usually lies free and can be teased out without difficulty The opening running down to the nucleus pulposus can then be demonstrated

Fig. 4.—Dura exposed. Mass can be palpated through the dura

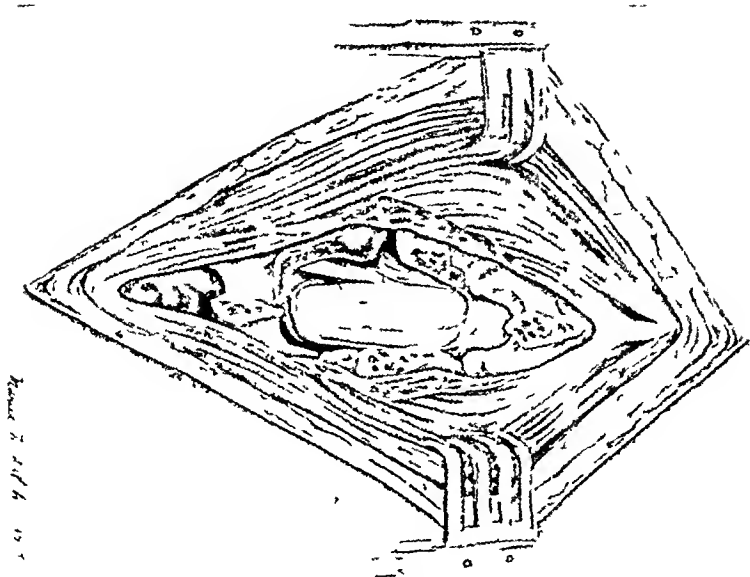


Fig. 5.—Lumbar portion of the cord drawn aside. Mass showing through the posterior longitudinal ligament

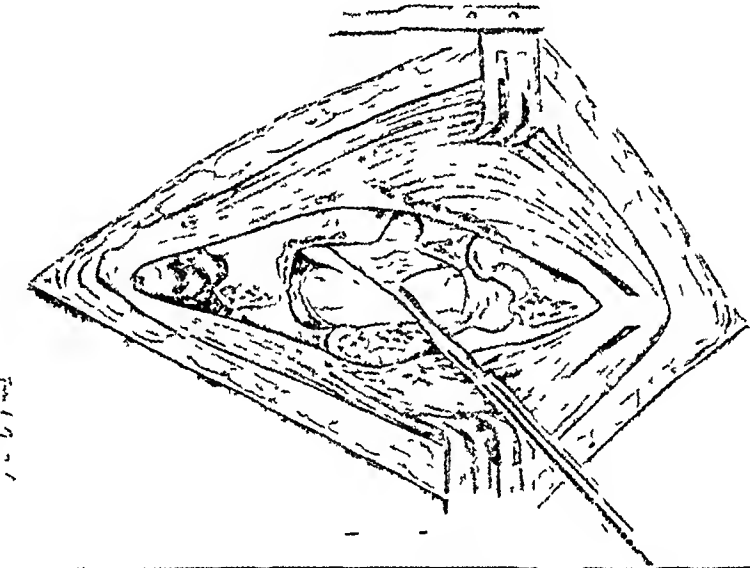
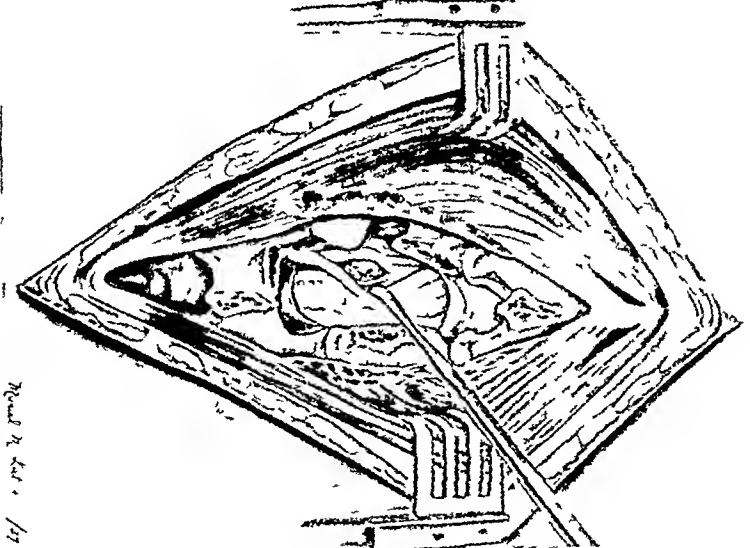


Fig. 6.—Posterior longitudinal ligament incised exposing the extruded fragments



Sometimes it is easier to remove the fragment by incising the dura posteriorly and again anteriorly and in many instances we have opened the dura simply to remove the lipiodol. If this is done the root or roots riding over the fragment can be inspected. It will be seen that the compressed root is distinctly reddened and edematous, unlike the rest of the cauda equina. In a few cases instead of a frank rupture with an extruded fragment we have found a general bulging of the whole edge of the intervertebral disk (Fig 7). It is as though the disk had been compressed and had mushroomed backward. Usually we have trimmed off some of the protruding disk where it seemed to compress the fifth root. In others we have contented ourselves with removing

the edge of the facet. These cases are not as satisfactory as those in which there is a frank rupture.

We have felt that any laminectomy must further weaken a spine already weakened by rupture of the disk. For this reason we have felt that some form of fusion is advisable in many instances. This is particularly true in patients who do heavy work. If fusion is indicated it is carried out by a member of the orthopedic department as soon as the fragment has been removed.

A surprising phenomenon that one notes in handling a group of these cases is the immediate relief obtained. Many times the patient will tell you that the pain in his leg is completely relieved as soon as he recovers from the effect of the anesthetic.

In all, we have operated upon 58 cases of rupture of one or another of the lumbar disks.

During the investigation of this subject, seven cases have been operated upon in which no abnormality of the disk was

FIG 7—General posterior bulging of the disk margin. That on the right is the most marked.

demonstrable. In three, chronic arachnoiditis was found and in four, no lesion within the spinal canal could be seen. In only two of these cases did the roentgenologic findings suggest a ruptured disk. In all the rest of these cases it was thought advisable to perform a lumbosacral fusion anyway and exploration of the spinal canal was the first step in the fusion operation.

This paper was written in order to present a group of cases suffering from intractable sciatic pain without paralysis or outstanding neurologic signs. The results obtained in this series, leaving out those with frank compression of the cauda equina, are summarized in Table IV.

RUPTURE OF INTERVERTEBRAL DISK

TABLE I

SEX AND AGE INCIDENCE

	Cases	Per Cent		
Female	13	22.6	Youngest	20
Male	45	77.4	Oldest	53
			Average	37
Totals	58	100		

TABLE II

LOCATION OF LESION

Disk between second and third lumbar vertebrae	1	
Disk between third and fourth lumbar vertebrae	4	
Disk between fourth and fifth lumbar vertebrae	35	60%
Disk between fifth lumbar and first sacral vertebrae	17	30%
Disk between first and second sacral vertebrae	1	
Total	58	

TABLE III

RESULTS IN ALL CASES

Well	32
Improved	14
Unimproved	2
Died, result of operation	1
Died, unimproved, urinary sepsis	1
Too recent to evaluate	8
Total	58

TABLE IV

CASES OF SCIATIC PAIN WITH MINOR NEUROLOGIC SIGNS

Ruptured intervertebral Disk	48
Well	29
Improved	10
Unimproved	1
Too recent to evaluate	8
Localized arachnoiditis	3
Negative explorations	4
Deaths	0
Total	55

CONCLUSIONS

Rupture of a lumbar intervertebral disk into the spinal canal, particularly the fourth or fifth, is a definite cause of sciatic pain

This is one of the few causes of sciatic pain in which compression of a nerve root can be demonstrated

The diagnosis can be made with great accuracy

The results of operative removal of the fragment are highly satisfactory

REFERENCES

- ¹ Mixter, W J, and Barr, J S Rupture of the Intervertebral Disc with Involvement of Spinal Canal *New England Jour Med*, 211, 210-215, 1934
- ² Mixter, W J, and Ayer, J B Herniation or Rupture of the Intervertebral Disc Into the Spinal Canal *New England Jour Med*, 213, 385-393, 1935
- ³ Goldthwait, J E The Lumbo-sacral Articulations, an Explanation of Many Cases of "Lumbago," "Sciatica" and Paraplegia *Boston Med and Surg Jour*, 164, 365-372, 1911
- ⁴ Middleton, G S, and Teacher, J H Injury of the Spinal Cord Due to Rupture of an Intervertebral Disc During Muscular Effort *Glasgow Med Jour*, 76, 1-6, 1911
- ⁵ Dandy, W E Loose Cartilage from Intervertebral Disc Simulating Tumor of Spinal Cord *Arch Surg*, 19, 660-672, 1929
- ⁶ Schmorl, G Die gesunde und kranke Wirbelsäule im Röntgenbild Pathologisch-anatomische Untersuchungen *Fortschr ad Geb d Röntgenstrahlen*, Ergänzungsband 43, Georg Thieme, Leipzig, 1932
- ⁷ Elsberg, C A Diagnosis and Treatment of Surgical Diseases of the Spinal Cord and Membranes W B Saunders Company, Philadelphia, 1916, p 238
- ⁸ Stookey, B Compression of Spinal Cord Due to Ventral Extradural Cervical Chondromas, Diagnosis and Surgical Treatment *Arch Neurol and Psychiat*, 20, 275-291, 1928
- ⁹ Hampton, Aubrey O, and Robinson, J Maurice The Roentgenographic Demonstration of Rupture of the Intervertebral Disc Into the Spinal Canal After the Injection of Lipiodol *Amer Jour of Roent*, 36, 782-803, December, 1936
- ¹⁰ Love, J G Protrusion of the Intervertebral Disc (Fibrocartilage) Into the Spinal Canal *Proceedings of the Staff Meetings of the Mayo Clinic* 11, No 34, August 19, 1936
- ¹¹ Barr, Joseph S "Sciatica" Caused by Intervertebral Disc Lesions A Report of Forty Cases of Rupture of the Intervertebral Disc Occurring in the Low Lumbar Spine and Causing Pressure on the Cauda Equina *Jour Bone and Joint Surg*, 19, No 2, 323-342, April, 1937

DISCUSSION—DR HOWARD C NAFTZIGER (San Francisco) Doctor Mixter deserves great credit for clarifying our ideas as to the cause, pathologic changes in and treatment of a considerable number of patients who suffer from low back pain and sciatica. Previous to Doctor Mixter's work, most neurologic surgeons probably had had the experience of operating occasionally for what had been diagnosed as an intraspinal neoplasm, and encountered instead a cartilaginous mass of one type or another. The underlying pathologic changes in these patients were not realized. Since Doctor Mixter called our attention to it, my associates and I have been greatly interested in the subject and have operated upon some 30 patients with this type of disturbance.

The material found and removed at operation is not pure cartilage, but fibrocartilage, usually stringy in appearance and much like chewed up chalk. The gradation of tissue between the nucleus pulposus and the annulus fibrosus is indefinite, and apparently circulatory changes in the intervertebral disk may occur at very early ages. Degenerative changes undoubtedly play an important part. Our patients have shown a little wider variation in age than Doctor Mixter's, the youngest being 18 and the oldest 63 years of age.

We have been greatly impressed that such a high percentage of the patients whom we have investigated for the cause of low back pain, or sciatica, or both, have proved to have organic changes—usually fibrocartilaginous of the disk, but sometimes alterations in the ligamentum flavum. In this group of patients with chronic severe symptoms, proved pathologic changes in the spinal canal

were found in more than one-half. I believe that we investigated no patients except those who had had prolonged treatment and, frequently, many recurrent attacks. Almost all of them had had strapping, manipulations, physiotherapy of various kinds, traction, casts, braces, *etc*

The industrial aspects of patients in this group will have to be thought of shortly. Not all of the patients have a history of a single severe trauma, some have had repeated lesser trauma, as from riding horse back, jumping, *etc*. There is, in addition, still a question as to what proportion of patients, who have had a low laminectomy or hemilaminectomy, will require fixation of the spine by bone graft. Perhaps there will be a considerable number, but certainly not all of these patients will have persisting disability, even for heavy work.

In our experience, the clinical picture varies greatly. In some instances there has been complete compression of the dural sac with involvement of all fibers passing from the dura below that level. Commonly there has been some pain in the back, but sciatica has been the leading feature. Frequently there is evidence of involvement of the fourth or fifth lumbar root with subjective or objective sensory alteration over the outer side of the leg in its lower two-thirds and extending over on to the dorsum of the foot. Muscles supplied by the external popliteal nerve also frequently show weakness and occasionally there is a disproportionate weakness of one or another muscle in this group. Often the extensor proprius or the tibialis anticus may seem disproportionately weak by comparison with the other extensors. It is a matter of considerable interest that complete remissions in the signs and symptoms of back pain and sciatica may occur and yet, ultimately, rupture of the intervertebral disk is found.

At operation, the cartilage is usually in a lateral position, slightly anterior to one of the nerve roots. Often they can be felt more readily than seen. Occasionally they are found in bizarre places. I recall one case in which a large mass of fibrocartilaginous material had herniated around the lateral side of the dura and had come to lie immediately beneath the lamina where it compressed the dural canal. Continuation of this mass around the dura led one to the opening in the intervertebral disk from which it originated. In another recent instance, a cartilage had penetrated the ventral surface of the dura and had come to lie inside it as a pedunculated mass.

Even after the laminae are removed, it is not always easy to recognize immediately these small protrusions of cartilage—and very small ones indeed may compress a root sufficiently to give severe symptoms. I am sure that we should have missed a considerable number if extradural exploration, which was negative, had not been followed by wide opening of the dura with careful retraction of the filaments of the cauda equina and inspection of the inner surface. In a considerable number we have thus located the rounded protrusion pushing into the dura, and usually there are minute telangiectases altering the appearance of the dura at that spot. Frequently the nerve root is compressed and often it is considerably swollen. We have removed a number of these cartilages by the transdural route, which oftentimes is easier than the extradural removal and is less vascular.

In several instances in which disease or injury of the intervertebral disk was suspected, we found instead alterations—thickening or fibrosis—in the ligamenta flava. One of my associates, Doctor Brown, recently operated upon a patient who had a complete transverse obstruction of the dural canal from such a cause.

Complete blockage of the canal is, of course, infrequent and small herniations compressing the root may give severe symptoms without noticeably

affecting the flow of lipiodol as seen under the fluoroscope. Unless the roentgenograms are taken in such a direction as to bring the indentation of the column of lipiodol into profile, the condition may be missed. Repeated studies are not infrequently necessary. We feel greatly dependent upon the roentgenologist.

Doctor Mixter's work has reduced the number of patients who have been treated unsatisfactorily in the past for conditions vaguely considered as lumbosacral or sacro-iliac disorders and has made the pathologic changes clear in a large proportion of them. In most of these patients the diagnosis is not difficult and the treatment is highly satisfactory.

DR KELLOGG SPEED (Chicago). Among the last 100 patients I have seen with complaint of back, thigh and leg pain, well described by Doctor Mixter, practically all with the history of trauma, five have continued to complain in spite of palliative treatment extending in some instances over a period of three years. One patient had a trisacral fusion. None had compression or other fracture of the spine. Three of these five patients were given lipiodol spinal injection after puncture, and all showed defects in the roentgenogram suggesting cartilage protrusion.

No xanthochromia or increased pressure of spinal fluid was found. Protein content varied from 20.2 to 34.8 mg. Cell counts were low or zero, and sugar determinations varied from 65 to 75.6 mg. There were no neurologic findings of cord tumor.

My experiences after such a low percentage of persisting symptoms leads me to believe that these patients with back and "sciatic" pain should be offered ordinary nonoperative treatment, including correction of focal infections, and injections with normal salt solution into the sacral plexus, followed by wearing a back brace for a while before lipiodol is injected intradurally. This oil may never absorb, and probably should not be injected unless it is to be abstracted later by open operation. I evaluate lasting atrophy of the thigh muscles along with pain as an indication for lipiodol injection.

Disk injury, or protrusion, concomitant with compression fracture, but not necessarily at the same level, may account for many of the long standing instances of back pain after compression fracture of the body of the vertebra, although hyperextension of the spine and a chance to recover bony support may be given. Mechanical analysis of the ordinary compression injury of the spine by flexion or direct pressure of the superimposed body weight, however, does not seem to explain a posterior protrusion of the intervertebral disk at the fracture level at the time of the fracture. The possibility of the congenital nature of these protrusions must be kept in mind, whether into the corpus of the vertebra, or posteriorly into the spinal canal, later to be aggravated by trauma.

Most of these patients have flat lumbar areas, or even lumbar kyphosis of years' duration. When a displaced disk is roentgenologically proven, it should be removed and a spinal fusion covering the defect caused by the operative approach for the removal and at least one segment of the spine above and below must be included.

DR WILLIAM JASON MIXTER (Boston), closing. Doctor Speed has spoken of his fear of the use of lipiodol. I also feel definite hesitation in using it, unless the indications seem clear. I believe that if these patients do not recover under palliative orthopedic treatment, the use of lipiodol is indicated. I have seen no permanent bad results from the use of lipiodol, there have been some cases of neuralgic pain reported following its use, but I do not think they are common.

It seems to me that the lesion of which we are speaking this morning is seldom associated with fracture of the vertebra, and that probably the cause is a different kind of trauma than that which causes a compression fracture of the vertebra

I like to theorize that it may be a direct pushing together of the two vertebral bodies rather than a bending crush. Some of our histories have pointed to that

Fusion, I think, should be used in most of the industrial cases, because we are expecting to return them to heavy work. I think most patients who do not work hard can probably get along perfectly well without fusion

The lateral view is of very little value, as Doctor Speed has said. Remember that the fifth root is compressed by the fourth disk, not the fourth root by the fourth disk. Always open the dura if you cannot find the mass outside

ANESTHESIA AND SURGERY

RALPH M. WATERS, M.D., AND ERWIN R. SCHMIDT, M.D.
MADISON, WIS.

FROM THE DEPARTMENTS OF ANESTHESIA AND SURGERY, UNIVERSITY OF WISCONSIN MEDICAL SCHOOL, MADISON, WIS.

ANTISEPSIS and later asepsis, together with anesthesia, made possible the development of modern surgery. Accepted by surgery, of the two it is only asepsis that was taken up whole-heartedly and developed. Anesthesia was gladly welcomed, but received little aid or stimulation either as an art or a science, by the surgical profession. Snow supplied a beginning scientific background for anesthesia, and, because the agents were potent enough to satisfy the demands of the surgeons, attempts to improve the status of anesthesia by medical men were frowned on by the surgical profession, and often deliberately hindered. This attitude placed anesthesia in the hands of young assistants who looked upon it as a necessary evil, a step, or a stage on their way to become a surgeon, or into the hands of the technician. This attitude has resulted in a distinct delay in the development of anesthesia as an art and a science.

The basis of this paper is derived from an association with medical men interested in the science and art of anesthesia, and is an attempt to correlate anesthesiology and surgery in a clinical way.

Anesthesia is produced by reducing the reflex activity of the nervous system. The reflex activity of the nervous system is directly proportional to the metabolic rate (Chart 1). Metabolic rate is variable, depending on sex, age, pain, emotion, fever, degree of muscular relaxation, and thyroid activity. The metabolic rate of a patient may be decreased by eliminating the factors of pain, nervous and muscular tension, thyroid activity, and fever. Pain and emotion are reduced by preoperative use of morphine, barbiturates, scopolamine, and nonvolatile drugs by mouth, hypodermic, *etc.* Thyroid activity, as in hyperthyroidism, is reduced by rest, food, sedation, and iodine. For each degree of fever, the metabolic rate is increased 7 to 8 per cent. If possible, the patient should wait for surgery until free from fever (Chart 2). These factors explain the reason for the varying amounts of agent necessary in the 100 per cent potent, and with the less potent agent demonstrate the impossibility of reaching a satisfactory stage of anesthesia (Chart 4).

The third stage of anesthesia has been divided into four planes (Chart 3). This has been made possible by observing certain physical signs as the anesthesia progresses up or down. Among these signs are the respiratory rate, the type of breathing, the abolition of the action of the intercostal muscles, the movement of the eyeball, the pupillary reaction with and without preoperative medication, the eyelid reflex, and the swallowing and vomiting reflex. The importance of making these finer divisions of the third stage becomes apparent

(Chart 2) Many operations do not need third or fourth plane anesthesia, and many operations need a third or fourth plane anesthesia only for a short period and for a certain stage of the operation. Twenty minutes of third plane anesthesia may be as hard on a patient as two hours of second plane anesthesia. Fourth plane anesthesia paralyzes the smooth muscle fibers of the blood vessels allowing the active circulating blood volume to be reduced and thus produces shock.

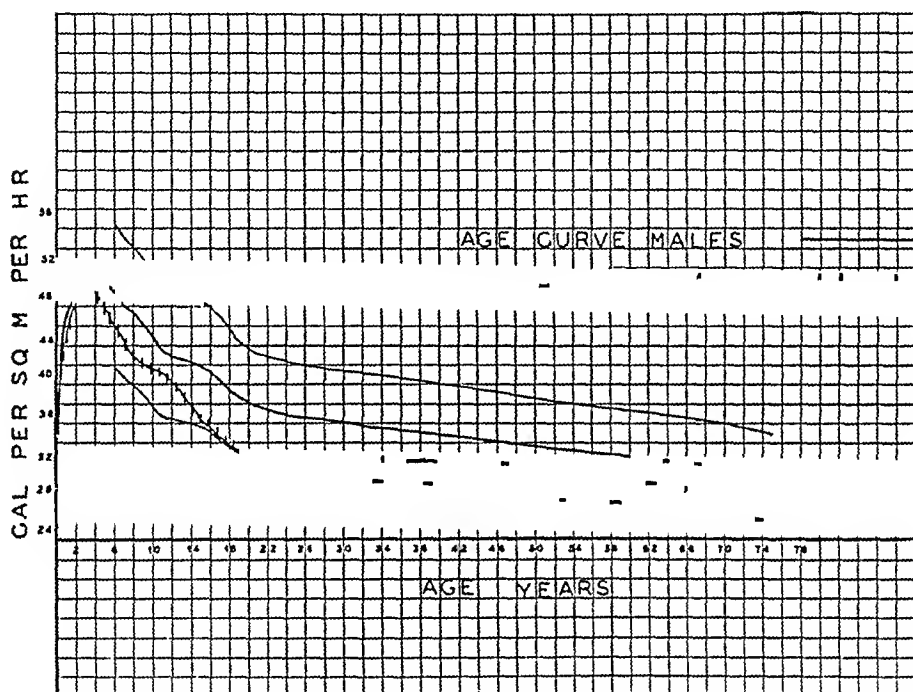


CHART 1.—The curves indicate the metabolic rate for male and female from birth to the seventh decade. The curve for males shows the limits of plus or minus variations of 15 per cent, which roughly delineates the range of "normal" variability. The curve for females is lower than that for the males. These curves from ages six to 75 reproduce the latest Mayo Clinic predictions¹ with the single difference that their absolute values have been lowered by constant percentage amounts necessary to fit them to the measurements on normal subjects made over a period of years at the University of Wisconsin and State of Wisconsin General Hospital.² The curves below six years are idealized continuations that follow the general trend of the classic smoothed curve of Aub and DuBois.³

The value of this finer distinction becomes more apparent in clinical surgery when we appreciate at what levels the various reflexes are abolished. It means a close cooperation between surgeon and anesthetist. As the operation progresses, the anesthetist can vary the depth of the anesthesia so as to eliminate the necessary reflexes to permit the performance of the operation, keeping the patient in the planes of anesthesia that are least harmful.

The various reflexes necessary to produce the clinical signs which are used in placing the level of anesthesia have been presented. A few other reflexes and the level at which they are abolished will be presented to show how these facts may be used to the advantage of the patient and the surgeon.

All reflexes as a result of skin trauma are abolished by anesthesia in the upper half of the first plane. Therefore for skin incisions this is sufficient.

The reflex contraction of skeletal muscle is in proportion to the size of the muscle, the amount of traction stimulus, and the suddenness with which the stimulus is applied. Gradual stretching produces little or no response, and long continued stretching will produce a temporary paralysis of the muscle. Lower second plane anesthesia will abolish skeletal muscle contraction. Traction reflexes arise as a result of tugging or pulling on visceral structures. These are proportional to suddenness and the strength of the stimulus. The excitation of these reflexes results in (1) Contraction of the abdominal wall with expulsion of the viscera, (2) stimulation of the respirations, and (3) adduction of the vocal cords. Even lower third plane anesthesia may not

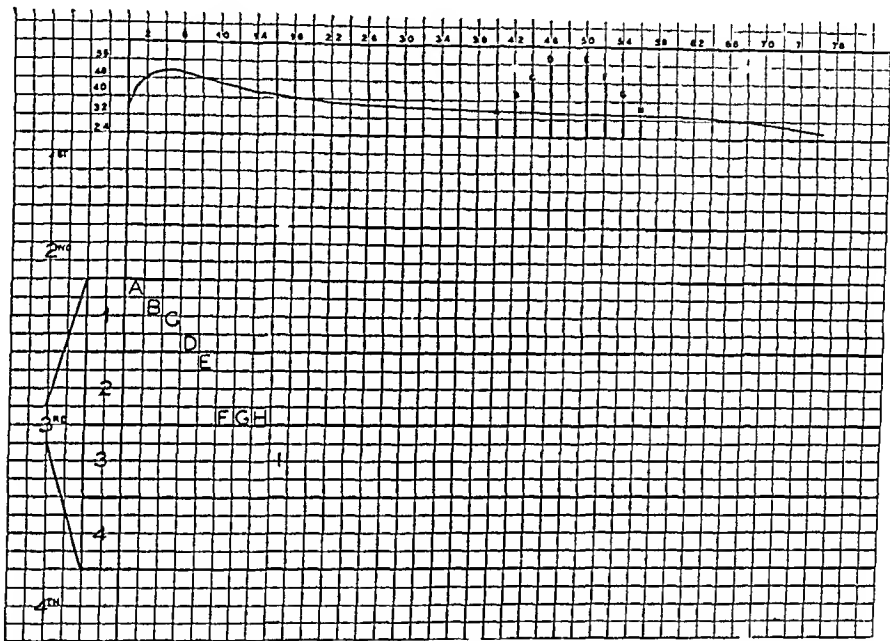


CHART 2—With a metabolic rate of 24 calories per sq Mm of body surface add the factor of fear and the rate is elevated as indicated by line A, pain will raise it as represented by line B, fever will give line C and thyroid activity will result in line D. To depress this rate, barbiturates the night before will eliminate fear and give line F, the emotions are allayed and line G results, and preoperative medication with morphine and scopolamine will result in a lower rate—a much easier patient to handle. *Levels of Anesthesia at Which Reflexes Are Abolished* (A) First part of first plane, third stage. Bruin bone, thyroid, breast, stomach, kidney, and other glandular tissues, except for traction reflexes from their coverings or attachments are abolished. (B) Upper half of first plane, third stage. Skin reflexes are usually abolished at this level. (C) Below middle of first plane, third stage. Pharyngeal reflex is abolished. (D) Lower border of first plane, third stage abolishes or renders negligible reflexes caused by injury to or cutting great sciatic nerve. (E) Junction of first and second planes, third stage abolishes cough reflex. (F, G and H) Lower level of second plane, third stage, abolishes or renders negligible muscle reflexes. The anal sphincter reflex may not be abolished by the fourth stage. The traction reflexes met with so frequently in abdominal surgery may be abolished but readily instituted by rough handling of the viscera. The subdiaphragmatic reflex, an adduction of the vocal cords usually upon expiration with a contraction of the abdominal muscles may be present in the third plane, then intubation is preferable to deeper anesthesia. (I) Third plane, third stage, abolishes tone of smooth muscle when it reaches the middle of the plane (Guedel¹).

abolish these reflexes, but skeletal muscle response is abolished at the lower part of the second plane. By making traction gently, slowly, and continuously, the reflexes may not be irritated, and the necessity for the lower third stage anesthesia with the attendant paralysis of smooth muscle never arises. This

is particularly true of the peritoneum. In closing an abdomen, application of forceps to the peritoneal edge and then pulling quickly on them stimulates these traction reflexes and changes the depth of anesthesia necessary from a second plane to a third plane or even deeper.

The upper plane of the first stage is sufficient to abolish the pain in surgical traumatism to bone, brain, thyroid, breast, kidney, spleen, liver, stomach, intestines and omentum. Their ligamentous attachments may be cut, burned,

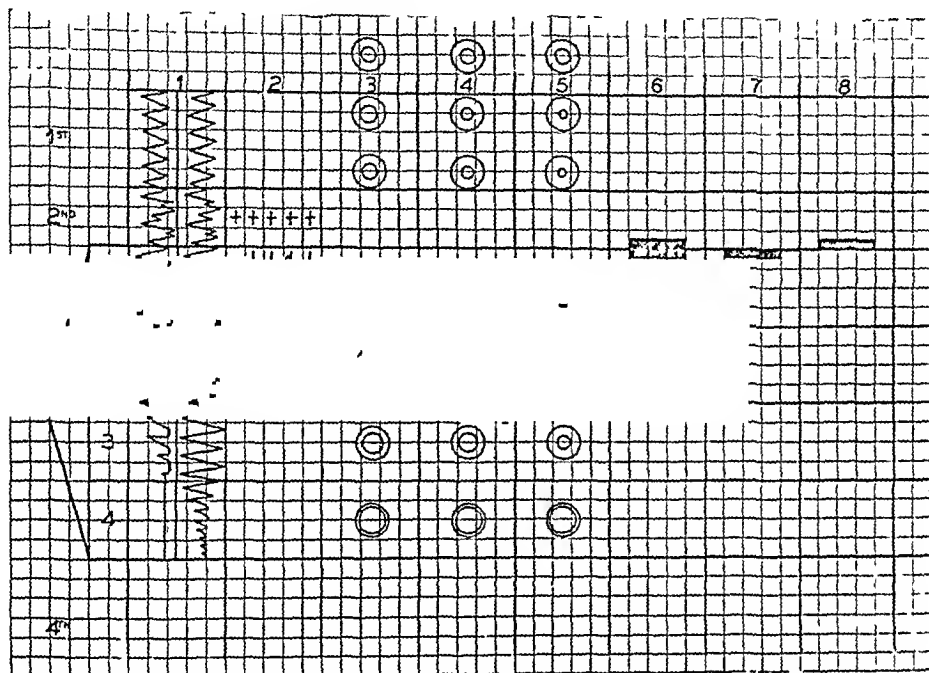


CHART 3—Column 1 shows the respiratory motion. During the first stage it is fairly regular. There may be variations as a result of fear or emotions. The second stage has irregular breathing and when it becomes smooth indicates that the second stage is being entered. This smoothness persists until the lower part of the second plane when there is a beginning paralysis of the intercostal muscles. This paralysis becomes complete at the end of the third plane. The respiratory movement continues to decrease and the volume is less until the fourth stage is reached when respiration completely ceases. Column 2 represents eyeball activity. During the second stage there is marked eyeball activity. This continues into the third stage and becomes less the farther the anesthesia descends into the first plane, ceasing as the second plane is encountered. Columns 3, 4 and 5 show the reaction of the pupil in the different stages to no preoperative medication, to morphine and scopolamine, and to morphine respectively. Column 6 shows the eyelid reflex which disappears as the third stage is entered. Column 7. In ascending anesthesia, as the patient reaches the upper part of the first plane of the second stage, the swallowing reflex returns, and as the second stage is reached the vomiting reflex becomes active (column 7). In descending anesthesia neither the swallowing nor vomiting reflexes are definitely placed (Guedel¹⁴)

or crushed. Traction will cause some pain. Yet to perform an operation that may require an hour, only five or ten minutes need a third plane anesthesia, the usual procedure is to use the deepest stage of anesthesia necessary for any part of the operation and use it for the whole period. With a knowledge of the levels of anesthesia at which reflexes are abolished a competent anesthetist can gauge the depth so as to spare the patient and permit the surgeon to perform the operation. A competent anesthetist working with a surgeon not appreciative of these facts means that the type of anesthesia here described is impossible.

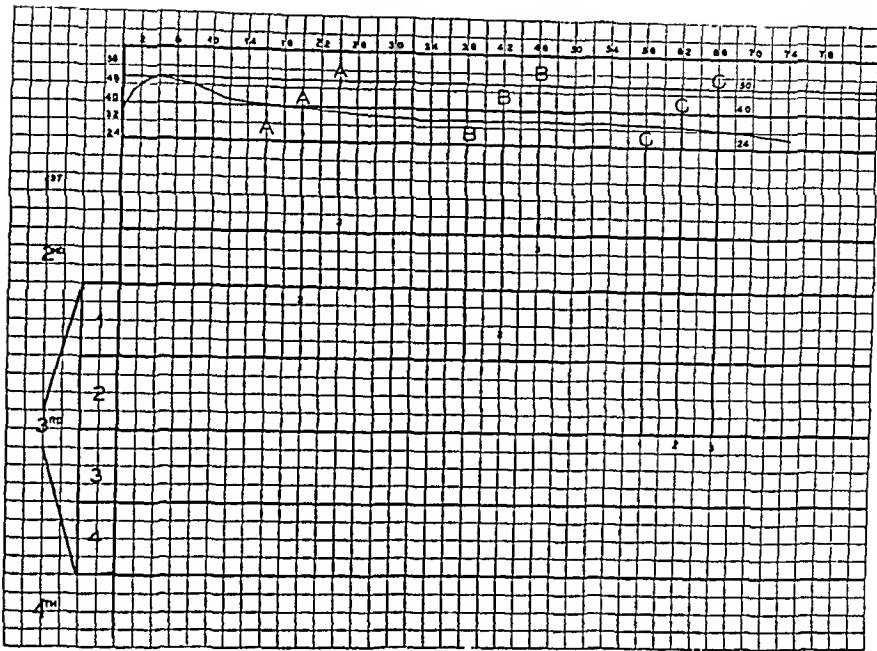


CHART 4—Nitrous oxide A 1—Starting at a metabolic rate of 24 calories per sq Mm of body surface will carry the anesthesia to the middle of the first plane of the third stage A 2—Metabolic rate at 40 calories per sq Mm surface will reach only to upper margin of the first plane A 3—Metabolic rate at 48 calories per sq Mm surface will reach the lower portion of the first stage Ethylene B 1—Metabolic rate of 24 calories per sq Mm surface reaches the lower edge of first plane third stage B 2—Metabolic rate of 40 calories per sq Mm surface reaches middle of first plane third stage B 3—Metabolic rate of 48 calories per sq Mm surface reaches lower portion of first stage One hundred per cent potent anesthetic agents as chloroform ether, vinyl ether cyclopropane and ethyl chloride can reach any depth of anesthesia the amount of agent necessary will vary as shown by lines C₁, C₂ and C₃ depending on metabolic rate (Guedel⁴)

REFERENCES

- ¹ Boothby, Walter M, Berkson, Joseph, and Dunn, Halbert L Am Jour Physiol, 116, No 2, 468-484, July, 1936
- ² Stark, Marian E Unpublished compilations
- ³ DuBois, E F Basal Metabolism in Health and Disease Lea and Febiger, 1936, p 150
- ⁴ Guedel, Arthur E Inhalation Anesthesia—A Fundamental Guide The Macmillan Company, New York, 1937

DISCUSSION —DR ARTHUR W ELTING (Albany, N Y) I think we can safely say that today we are witnessing the birth of the science of anesthesiology It is rather striking that over a large number of years there have been comparatively few papers presented to this Association on the general subject or the more intimate problems of anesthesia I think in large measure that represents about the relative interest that the profession at large has taken in the subject of anesthesia

As I remarked a few years ago on an occasion in New York, the reason why a large part of the anesthesia in this country is being administered by the trained nurse anesthetist was because the medical profession had failed in their job The institutions of learning in medicine had not developed the proper teaching facilities The profession, particularly we surgeons, had not demanded in our institutions properly organized properly developed and controlled departments of anesthesia Even today in very few institutions in this country are there such departments but in some there are, and the heads of these departments are the forward looking men in the problem of anes-

thetia, its development for its practical avail to the patients and the surgeon, and for its usefulness in the training of doctors to give anesthetics

I think we will all welcome the day when anesthesia in general is administered by the medical profession. That day, I believe, is not so far distant, not that I expect nurse technicians to disappear perhaps for a long time, because they have certainly been most effective and most efficient but under the direction of a properly trained physician at the head of a department of anesthesia, their activities will become increasingly more useful.

It may be of interest to you to realize, as members of the American Surgical Association, that the first affiliated board to be recognized by the American Board of Surgery is the Board of Anesthesiology. Anesthesiology therefore, becomes essentially the godchild of the American Surgical Association, and it seems to me that it is our duty as members of the American Surgical Association to further in every possible way the efforts of this small group at present, but soon to be a larger group, of men who have devoted their interests, their time and their lives to the development of the science of anesthesiology.

Many of us have been more or less afraid of the possibilities of legislation in relation to anesthesia. Over the length and breadth of the country legislatures have been considering, and in one way or another threatening to limit us in the control of our anesthetic problems. I can assure you that this group who today represent the science of anesthesiology, who have been recognized by your Board, are a group of men from whom we shall expect to secure not legislation, but increasing education to the benefit of the patient and the surgeon.

DR RALPH WATERS (Madison, Wis.) closing. Doctor Schmidt and I simply wish to make a plea for a little more cooperation between surgeons and the subject of anesthesia. Chronologically, the scope of the duty of the surgeon, like that of the whole medical profession, has progressed along a gradually widening road. In the long past the surgeon was concerned with the elimination of diseased tissue. Such removal implied first to cut it open then to cut it off, and now, I take it, to cut it out. Both patient and surgeon were then satisfied if there was no pain and if death did not result.

The present day surgeon is, and the future surgeon will be, concerned with much in addition to the old duties of removing pathologic tissue. He will remodel the body and rewire the physiologic currents of life, not so much to prevent death, as to make living more abundant.

With such an aim, surgery can no longer depend for pain relief upon the anesthetic practices of former years. Pain relief must develop into a science, anesthesiology, if you will, a sister effort which will keep pace with the rapidly developing knowledge of the physiologic mechanisms of life so that it may speak a common language, with the modern surgeon on the one hand, and with the diagnostician and the laboratory on the other. In the light of developing physiologic discovery, new methods of pain relief must be devised and more logical use of old ones must be provided to serve as a foundation for the ever widening pathway of the surgery of the future. But that is not all. The anesthetist should and can have much help to offer the surgeon in addition to pain relief. Comprehensive care of patients during operation, rational supervision of therapy with gases and vapors, the blocking of certain anatomic regions, the intravenous administration of various substances—all may at times be advantageously entrusted to the anesthetist. The liaison between pharmacology on the one hand and surgery on the other can to a large extent come through anesthesiology.

Anesthesia and anesthetists, to date, can claim only a little progress other than a nucleus of enthusiastic pioneers who are willing and anxious to devote their lives to the development of a science of anesthesia. The helping hand of such a group as this, of which I am a guest, may mean a great deal. Most of you are teachers of surgery. Our schools have drifted toward a neglect of the teaching of anesthesia at a period in scientific progress when such teaching is paramount. Some of you have tried utilizing young surgeons, young internists, and others as instructors in anesthesia and as directors of departments of anesthesia. Such plans have not worked, I fear, because the subject is too broad and too deep. The pharmacology and physiology of anesthesia must be interpreted clinically by individuals with at least a modicum of clinical knowledge and clinical experience.

Doctor Schmidt and I wish to leave with you not the idea that we, at Wisconsin, have solved the problem of anesthesia—far from it—but rather that the problem exists and that it must be met in every medical school and in every medical center. The sooner all of you tackle this problem, the less lonesome those of us who have made a beginning will feel.

MEMOIR

LIEUTENANT-GENERAL SIR ALFRED KEOGH, G C B ,
G C V O , C H .

1857-1936

SIR ALFRED KEOGH was born in Dublin on July 3, 1857, and died July 30, 1936. His father was a member of the Irish Bar and Resident Magistrate



LIEUTENANT-GENERAL SIR ALFRED KEOGH G C B , G C V O C H

of Roscommon. He was educated at Queen's College, Galway, and at the age of 21 took his medical degrees at the Royal University of Ireland. Coming then to London he obtained a resident appointment at the Brompton Hospital for Consumption, and was for a time a Clinical Assistant at the Westminster Ophthalmic Hospital. In 1880, he entered the Army Medical Service and at Netley distinguished himself by taking the Herbert Prize and the Martin Memorial Gold Medal. After a period of service abroad he returned home and was appointed Medical Officer to the Royal Arsenal at Woolwich.

In 1900, he was promoted Lieutenant-Colonel. On December 2, 1904, he was promoted Colonel and on the following day Surgeon-General, and on January 1, 1905, Surgeon-General ranking as Lieutenant-General on being appointed Director-General, Army Medical Services. He remained Director-General from January, 1905, to March, 1910. In October, 1914, he was re-appointed Director-General shortly after the outbreak of the Great War and remained so until 1918.

Sir Alfred Keogh will be long remembered as a great administrator. He had all the requisites for the task. Quick perception of essentials, tenacity, enthusiasm and rapid action characterized all his work. His judgment was rarely at fault, it has been described as intuitive. Intuition there was, but it was founded on knowledge, wide reading and close observation.

In his younger days he devoted himself to acquiring a sound professional ground work, taking clinical appointments in general and special hospitals, and losing no opportunity of adding to his store. This professional keenness he kept up through his working life. I well remember how deeply interested he was when once on leave at Berne we paid a visit to Kocher, then on the crest of the wave of his European reputation. It was difficult to see which was the more absorbed, Kocher in demonstrating the work in his clinic or Keogh in eliciting all the information he could.

On joining the Army, without loosening his grasp on his purely professional work, Keogh immersed himself in the study of military medical problems. He familiarized himself with the various Commissions which had reported on the subject—especially the Herbert, Camperdown, and Elgin reports. In these, he would say, are laid bare most of the spots where the shoe pinched.

One of his great ambitions was to break down the barrier which existed between the civil and military branches of the profession. This was difficult so long as the military training center was isolated at Netley, but when he reached higher administrative rank the opportunity came and he seized it with both hands. By great good fortune the Secretary of State for War at the time (Mr Broderick, now Lord Middleton) was sympathetic and the Royal Army Medical College was built and opened in London. Thus the way to the cooperation of the civil and military branches of the profession, which has since proved of such great advantage, was opened. In this con-

nection the help that the then Advisory Board was able to give, and gave, should not be overlooked

In this College the postgraduate instruction for Captains for promotion to Major was expanded to nine months and the students were given the advantage of participating in the instruction given in the London schools and hospitals—and of training for specialties which they might wish to adopt

When the Territorial Force was established by Mr Haldane (later Lord Haldane) it became necessary to organize its Medical Service. This was more of a creative effort than an organization, as the medical units required for the Force did not exist, and the few medical units in being bore no relation to it

By visiting the chief medical centers in the Kingdom and expounding the meaning of, and the necessity for, these units, Keogh enlisted the cooperation of the leaders of the profession. The units were established, and courses of instruction were instituted, so that in 1914, when the War broke out, the great hospitals came into being without trouble and the sick and wounded were assured of the ministrations of the cream of the medical profession throughout the land

Another reform was the reorganization of the military hospitals at home. At the time he took over the office of Director-General every little dépôt station had its little hospital with a skeleton staff, in which cases of sickness occurring in the station, serious or slight, were supposed to be treated. These tiny hospitals were closed down, and all cases requiring hospital treatment were transported to the nearest well equipped hospital, where they could obtain the nursing and attention they required

A subject on which Keogh held strong and clear views was sanitation. His views did not at first meet with general acceptance, but they prevailed in the end. He held that the real sanitary officer of a unit was the Commanding Officer, not the Medical Officer. The preservation of the health of his men should be one of the main preoccupations of the Commanding Officer, the Medical Officer was there as an expert, to advise and to be consulted, but the ordinary rules of hygiene should be known to and enforced by all officers. For that reason it was necessary that they should all be instructed in these matters. Hence arose the School of Army Sanitation and the teaching the elements of Hygiene embodied in the Manual of Army Sanitation to all officers

Shortly after laying down his office as Director-General he was appointed Rector of the Imperial College of Science and Technology. This was a congenial post as his interests in Science had always been deep and close, and he welcomed the opportunity of extending its practical application. What he valued highly was the personal association into which he was brought with leading scientists, and with the students being educated at the College for scientific careers. With his keen sympathy for youth he was always on the lookout for measures which might enhance or ease the course of training

When the War broke out it was felt that his services were required in the military sphere. The British Red Cross Society, mindful of the way he had always encouraged and helped them during his tenure at the War Office, appointed him then Chief Commissioner in France and there he remained until October, 1914, when he was recalled and reappointed Director-General, Army Medical Services, at the War Office.

There he was able to see the reorganization of the Military Medical Service, which he had carried through in his previous tenure, come to fruition. The great machine started and worked without a hitch. There was complete and loyal cooperation between the civil and military sides. All had been made to understand and labored sympathetically to a common end. And so, with his hand on the lever, the machine continued to work until the close.

A great triumph, which was universally acknowledged. At the conclusion of the War all vied to do him honor.

At home he was made G C B (the first Army Medical Officer to be given that honor), G C V O and Companion of Honor, France made him Grand Officer of the Legion of Honor, Belgium Grand Officer of the Order of the Crown, Servia Grand Officer of the Crown, White Eagle, the Universities of Oxford, Edinburgh, Aberdeen and Leeds gave him honorary degrees, the Royal Colleges of Surgeons of England, Edinburgh and Dublin gave their Honorary Fellowships, and thus amid a chorus of appreciation he returned to his work at the Imperial College of Science and Technology.

As a man he was entirely likeable. Quiet, kindly and sympathetic in manner, no trouble was too great for him to help a friend or any one who applied to him for advice or assistance.

He possessed in a high degree the faculty of clear exposition and admired it greatly in others. He has told how, at times when working in London, he would steal off to the Law Courts to listen to some leading barrister presenting his case. A very distinguished retired official who did some work for him during the War once said of him: "In a long official career I have served many masters, but two stand out preeminently. Each had the power of stating lucidly not only what he wanted done but also of indicating categorically how he wanted it done. There was never any ambiguity. One was Lord Curzon of Kedleston and the other Sir Alfred Keogh."

A hard worker himself, Keogh expected hard work of those under him but he never failed to acknowledge such work with a kindly smile or a few words of appreciation, and took care that the credit went to the doer. Among those who worked under him, Keogh inspired feelings of intense loyalty and often of affection.

His work is done but his memory will long remain green among those who knew him.

This obituary has been written by Major-General Sir Michael Russell, K C M G, C B

APPRECIATION

BY LIEUTENANT-GENERAL SIR JAMES A HARTIGAN K C B, C M G
D S O, K H P

Director-General, Army Medical Services

ALTHOUGH Sir Alfred Keogh was personally unknown to the majority of serving officers of the Corps, the striking tributes paid to his memory in the Press have been, I feel sure, a source of much gratification to all its past and present members

Until the last couple of years of his life my acquaintanceship with him was limited to a single meeting in the South African War when I took a convoy of sick and wounded to the General Hospital which he commanded at Pretoria and when as a subaltern I was much impressed by the courtesy and hospitality which he showed me. I had since heard so much about him from officers who knew him well that I had come to regard him as one of the most outstanding officers of our Service

When, some two years ago, I heard that he had returned to London (he had been living abroad) I called on him, a very simple act of courtesy from a Director-General to the greatest of his predecessors. He was frankly pleased, and such was the modesty of the man that he seemed surprised to learn that his services were still remembered and appreciated. He invited me to visit him frequently and this invitation I took full advantage of, sometimes in order to seek his advice, which he gladly gave. I shall always entertain the happiest recollections of these visits. Seated on a chair with a rug over his knees, he would recount his experiences during the two periods in which he was Director-General—probably two of the most important periods in the history of the British Army as they were assuredly the most important in the history of the R A M C

The transfer of the College from Netley to Millbank, the organization of the Territorial Army Medical Service, the establishment of the School of Hygiene, the development of the clinical and scientific side of the Corps, liaison with the civil profession, his interview with Lord Kitchener before returning to the War Office for the second time—these were some of the topics which he related to me and which I found of absorbing interest. I invariably came away from these visits with the feeling that I had been in the presence of a great man

He retained the keenest interest in the Corps to the end, in fact, when speaking of it, he was inclined to forget he was an invalid (he was prone to anginal attacks) and allowed himself to be carried away by his enthusiasm. Before returning to take up the duties of Director-General during the War he asked for, and was accorded, exceptional powers, without which he could not have carried out that stupendous task

It is well known that his position at the War Office was somewhat unique. With Mr Haldane (afterwards Lord Haldane) he was on terms of close

intimacy. Their outlook and ideas had much in common and he always expressed the warmest regard and affection for that great statesman. With Lord Kitchener too he worked in the greatest harmony.

The sympathy of the whole Corps will go out to Lady Keogh and her family at the irreparable loss they have suffered and the nation in general, and we of his Service in particular may feel grateful that at the time of our greatest trial the post of Director-General was held by an officer who was so preeminently qualified to fill it.

ERRATUM

In the September issue on page 405, the Discussion of the paper "Regional Ileitis and Fibroplastic Appendicitis" by Doctors Ravdin and Rhoads, was through an error credited to Dr. Damon Pfeiffer. It should have been credited to Richard H. Meade, Jr., M.D.

EDITORIAL ADDRESS

Original typed manuscripts and illustrations submitted to this Journal should be forwarded prepaid, at the author's risk, to the Chairman of the Editorial Board of the ANNALS OF SURGERY

Walter Estell Lee, M.D.
1833 Pine Street, Philadelphia, Pa.

Contributions in a foreign language when accepted will be translated and published in English.

Exchanges and Books for Review should be sent to James T. Pilcher, M.D., Managing Editor, 121 Gates Avenue, Brooklyn, N.Y.

Subscriptions, advertising and all business communications should be addressed

ANNALS OF SURGERY
227 South Sixth Street, Philadelphia, Pa.

RESULTS with ALLANTOIN (NATIONAL) in the Treatment of Extensive Infected Burns



Case L S, age 16, showing burns prior to treatment with Allantoin

Abstract Case Report*—L S, extensive infected burns of shoulder, arms, hands and body from explosion of gasoline torch. Non-medical treatment for two months due to economical conditions. On admission to hospital skin completely gone. Unguents and oils with moist and dry heat ineffective. Most pinch grafts implanted on shoulder, in hope of new tissue formation so amputation below shoulder could be performed, died, remaining grafts did not spread. After several months the areas, as shown, were unhealed and covered with

purulent exudate. *Case record and detailed report with Allantoin literature mailed on request.

Treatment with Allantoin Ointment was first applied to sterile wax paper and then brought into contact with the denuded area. Epithelization began almost immediately. Young granulations advanced rapidly when treated intermittently with dry heat. Allantoin was used periodically when the tissues seemed to be lagging in their growth.

ALLANTOIN OINTMENT is of value in treating infected and slow healing wounds, varicose and other sluggishly healing ulcers.

THE NATIONAL DRUG COMPANY
BIOLOGICALS PHARMACEUTICALS BIOCHEMICALS
PHILADELPHIA, U S A

Same case, L S, showing new healthy tissue after treatment with Allantoin



-2 BOOKS
that make
IMPORTANT
NEWS!

DISABILITY EVALUATION

Principles of Treatment of Compensable Injuries

A NEW EDITION

Earl D. McBride, MD, FACS

*Assistant Professor in Orthopedic Surgery
University of Oklahoma School of Medicine*

TODAY the physician is called upon constantly to interpret in exact terms the alterations caused by injury to the motor structures. The difference of opinion of medical men on this subject makes this book especially valuable because Dr. McBride definitely evaluates the extent of functional loss from the economic standpoint and formulates a system of arriving at percentages of disability. He demonstrates how the physician's expressed opinion may be based upon the same scientific reasons as are used at arriving at any medical diagnosis—and how the anatomic alterations may be determined, the progress of improvement prognosticated, the final healing state recognized and the extent of the personal incapacity estimated with arithmetical preciseness. The author further clearly explains a method of appraising the extent of incapacity and evaluates the differences in the victim's condition before and after the injury and also determines the loss of function by evaluating the factors which compose function. This new edition will be ready October 25. 723 pages—374 illustrations—New (2nd) edition \$8.00

DISEASES OF THE BLOOD AND ATLAS OF HEMATOLOGY

By Roy R. Kracke, MD

*Professor of Pathology and Laboratory Medicine, Emory University
School of Medicine and Hortense E. Garner, MS*

ALTHOUGH just published, this book is already considered by authorities as the foremost volume on blood diseases. Dr. Kracke has long been acclaimed one of the outstanding men in this difficult field. Beginning with a complete description of the blood cells, the book then turns to Leukocytosis and Leukopenia and a detailed account of every form of anemia, pernicious anemia and the anemias of children. *In fact, no other book offers so complete a discussion of the anemias.* There is a complete classification of the Leukemias and Hemorrhagic findings. Chapters are included on bone marrow findings, malaria, blood groups and transfusions. Everything known and every theory which has gained acceptance of the normal blood as well as blood diseases is given with complete, detailed diagrams. The Atlas of Hematology superbly reproduces over 300 individual cells in full color and also contains 30 full pages of color plates of all the known blood diseases. *A book every general practitioner, specialist and laboratory must have.* 452 pages \$15.00

IF you have not yet had a chance to examine Lippincott's new magazine **DIGEST OF TREATMENT**, send today for a free sample copy. Every month it brings you the vital up-to-the-minute digest of developments in treatment culled by practicing physicians from over 230 of the world's foremost medical journals.

Published by **J. B. LIPPINCOTT COMPANY**

East Washington Square
Philadelphia

This is No. 7 in a series based on historical events in the development of radiography

...With the World War Came Dupli-Tized Film



THE World War, creating a shortage of glass for photographic purposes, crystallized extensive research and experiment to discover a new-type support for x-ray emulsion. The problem: To find a substitute substance that was glass-clear and would not buckle.

The first development—a cellulose nitrate sheet, coated with a single emulsion—did not prove satisfactory. Further research and more experiment followed. And 1918 saw practical achievement—a cellulose base that was double-coated. This was Eastman Dupli-Tized X-ray Film which made possible double-screen technique.

(Left) Loading double-screen cassette—common procedure today, made possible by Dupli-Tized X-ray film.

THUS was achieved the basis for the most revolutionary change in radiographic routine for present-day technical efficiency and accuracy. And no development in the progress of radiography had greater diagnostic significance.

With the double-screen technique as a foundation, the application of the x-rays expanded with amazing rapidity. The result is radiography as it is practiced today—an exacting science that con-

tributes to every branch of medicine. Whenever the problem is one of differential diagnosis, x-ray examination is practically indispensable. When intervention is necessary, it alone can provide a graphic guide as well as a visual record.

For both the patient and the physician, there is no more important safeguard than thorough radiographic examination. Eastman Kodak Company, Medical Division, Rochester, N. Y.

RADIOGRAPHS PROVIDE DIAGNOSTIC FACTS

IMPORTANT NEW PUBLICATIONS

NEW WORK

JUST READY

THE OCULAR FUNDUS IN DIAGNOSIS AND TREATMENT

By DONALD T. ATKINSON, M.D., F.A.C.S.

Consulting Ophthalmologist to the Santa Rosa Infirmary and the Nix Hospital San Antonio Texas
Fellow of the American Academy of Ophthalmology and Oto Laryngology*Imperial octavo, 259 pages, illustrated with 106 engravings including 58 colored plates
Cloth, \$10 00, net*

This work clearly outlines the general characteristics of the ocular fundus in health and disease. It is invaluable to everyone who uses the ophthalmoscope in diagnosis—to neurologists, obstetricians and surgeons as well as to ophthalmologists. Its outstanding feature is the inclusion of 58 colored plates prepared by the author, who is himself an artist and produces exactly what he interprets from the fundus and hence presents a more accurate picture than could a professional artist working from descriptions. Each plate is accompanied by descriptive matter, necessarily brief, but showing the clinical findings and laboratory reports that have a direct bearing upon the conditions illustrated. In addition to these colored plates there are 48 drawings in black and white also prepared by the author. This comprehensive, well organized material will be a distinct aid in the diagnosis of conditions revealed by the ophthalmoscope.

NEW WORK

JUST READY

ENDOCRINOLOGY

Clinical Application and Treatment

By AUGUST A. WERNER, M.D., F.A.C.P.

Assistant Professor of Internal Medicine, St. Louis University School of Medicine, Associate Physician, St. Mary's Group of Hospitals, Physician Endocrine Clinic, St. Louis City Hospital, Staff Member, St. Louis City Hospital Sanitarium and Infirmary, St. Louis Training School for Mentally Defective Children and the Missouri State Hospital, No. 1, Fulton, Missouri

Octavo, 672 pages, illustrated with 265 engravings. Cloth, \$8 50, net

This work summarizes what is actually known in endocrinology, systematizes our present knowledge of the normal and abnormal physiology of the ductless glands, shows the physical types resulting from endocrine disorder and applies this information to the recognition of the endocrine syndromes. The author presents the necessary fundamentals for diagnosis and treatment—the knowledge of the anatomical structure and arrangement of the autonomic nervous system, the study of the functions of the endocrine glands and the recognition of those vital processes of the body over which we have no control. After a discussion of metabolism and the glands in general, the function of each of the endocrines is considered and the known or postulated hormones are listed. In the treatment of the endocrine conditions the author advocates preparations and methods that have proved their efficiency, recognizing the variation in potency of the hormonal preparations and the difficulty of determining individual doses. The immediate objective of the work is to make clinical endocrinology more understandable to the physician, to point the way to correct diagnosis and to offer help in the relief of these ailments based on his personal experience.

NEW (3rd) EDITION

JUST READY

MODERN UROLOGY

In Original Contributions by American Authors

Edited by HUGH CABOT, M.D., LL.D., CMG, F.A.C.S.

Professor of Surgery, The Mayo Foundation, Graduate School of the University of Minnesota, and
Consulting Surgeon to the Mayo Clinic, Rochester, Minnesota*Two octavo volumes totaling 1813 pages, illustrated with 920 engravings and 21 plates. Cloth, \$20 00, net*

Since the last edition of this encyclopedic work appeared there have been great advances in technique and radical changes in conception. The revision of the text has been correspondingly radical. So extensively has it been rewritten that it is practically a new work. The contributors present the widest possible representation of urologic opinion in America. They include the leading diagnosticians, therapists, surgeons and pathologists in this field—men whose reputations are based on their accomplishments and whose opinions and conclusions may be accepted without question. The illustrations are profuse and for the most part original, portraying the various operative steps. In its present form this text is a comprehensive, scholarly, authoritative study. It is thoroughly modern in its spirit and material but soundly conservative in its principles and practice.

LEA & FEBIGER

WASHINGTON SQUARE
PHILADELPHIA, PA.

Please send me

☐ Atkinson's The Ocular Fundus☐ Werner's Endocrinology

\$10 00

8 50

||

☐ Cabot's Modern Urology Two Vols

\$20 00

☐ New Catalogue

Address

Name

(A. of S. 10 37)

20

Please mention ANNALS OF SURGERY when writing advertisers



FORTY YEARS *is a Long Time....*

Therapeutic products have come and gone—but Urotropin has survived on merit alone. That is something to 'crow about.' Today, Urotropin still retains the esteem of physicians as a urinary antiseptic which, used properly, is effective often where other measures have failed. Urotropin is a brand of methenamine, its purity guaranteed by Schering & Glatz, Inc. Supplied in sanitape protection in 5-gram tablets, 30 in a box; 7½-gram tablets, 20 in a box. Also in larger packages and in crystals. A trial supply may be obtained by physicians.



UROTROPIN

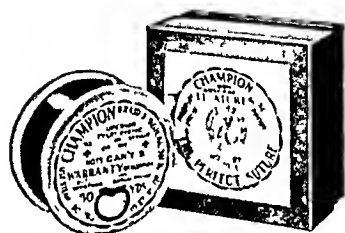
SCHERING & GLATZ, INC.
113 West 18th Street New York City

Less HOSPITALIZATION

More Cash in the Hospital's Bank Account

The use of Champion Serum-Proof Silk Sutures decreases the days required for tissue healing—hence, less cost for hospitalization

This is still another reason why Champion Serum-Proof Braided Silk Sutures are the least costly suture material available for internal or skin suturing. It is non-acid, non-irritating, benign to tissue, strong, supple



Free Operating Lengths on Request
State Sizes Desired

GUDEBROD BROS. SILK CO.

Founded 1870

PHILADELPHIA, PA

NEW YORK

CHICAGO

LOS ANGELES

BALTIMORE

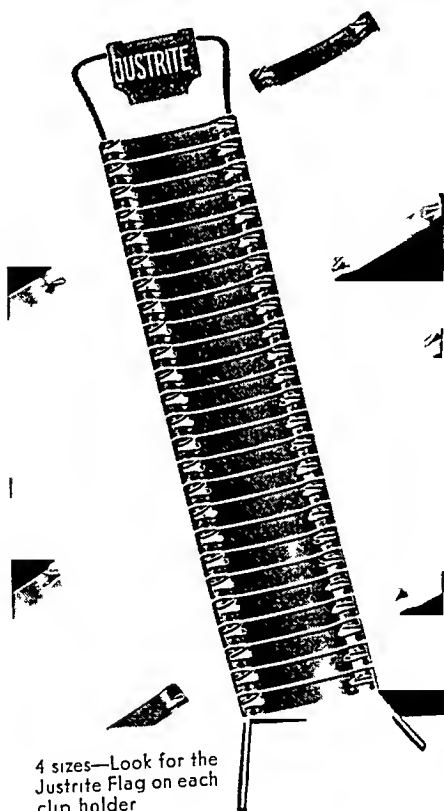
JUSTRITE WOUND CLIPS

for Ideal Wound Closure

JUSTRITE BENDING STRENGTH—firm enough to work with and soft enough so that only normal pressure is necessary

JUSTRITE ALLOY OF METAL—a carefully chosen non-rusting alloy always uniform

JUSTRITE SHARP POINTS—are placed at an angle to pierce and hold only the superficial skin. No bleeding or discomfort. Wounds heal quickly. Justrite is the ideal clip for skin suturing by the Michel Method.



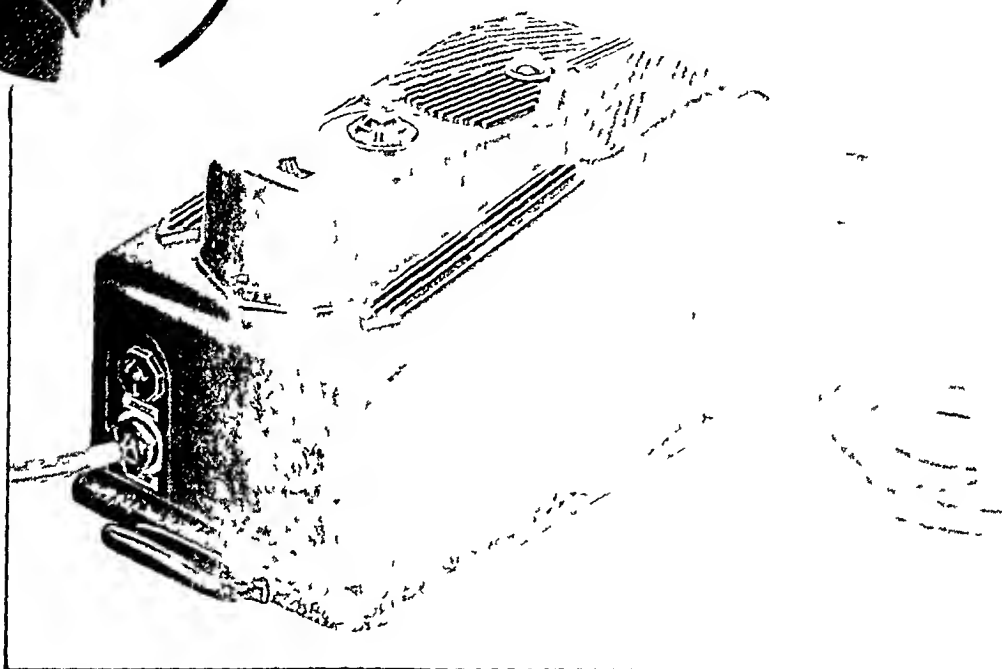
4 sizes—Look for the Justrite Flag on each clip holder

CLAY-ADAMS CO., INC.

25 EAST 26TH STREET, NEW YORK



ALLEVIATES PAIN—SPEEDS REPAIR IN TRAUMATIC INJURIES



INDUCTOTHERMY, by virtue of its basic electrical principle—electromagnetic induction—does what other forms of heating cannot do . . . GENERATES BENEFICENT HEAT WHERE HEAT IS MOST NEEDED, DEEP IN THE VASCULAR TISSUES AND MUSCLE. Skin and subcutaneous fat are affected but little.

Thus Inductothermy, as the main or adjuvant measure of treating the many TRAUMATIC INJURIES which every physician meets in his practise, ACCOMPLISHES MORE, DOES IT ECONOMICALLY, AND WITH UTMOST EASE OF APPLICATION AND OPERATION.

Learn at first hand what ownership of a G-E Inductotherm would ADD to your practise. OPERATE IT IN OWN YOUR OFFICE, AT YOUR CONVENIENCE, WITHOUT INCURRING OBLIGATION. Detach and mail the convenient coupon—now.

GENERAL ELECTRIC X-RAY CORP
2012 JACKSON BLVD, CHICAGO, ILL

I am particularly interested in how Inductothermy would help me in treatment of traumatic injuries. Have your local representative arrange with me for a demonstration of the Inductotherm in my office.

P210

Name.

Address

City.

**GENERAL  ELECTRIC
X-RAY CORPORATION**

2012 JACKSON BLVD

CHICAGO ILLINOIS

Proliferol

3 Solutions Available
Proliferol "A" "B" & "T"
Write for Booklet A10 on Technique
and Considerations in Treatment

Is the solution for the **INJECTION TREATMENT of HERNIA**

preferred by University Clinics and Leading
Surgeons with extensive experience in this
form of treatment

From the Laboratories of

ULMER PHARMACAL COMPANY
MINNEAPOLIS Manufacturing Chemists MINNESOTA

MODERN SURGICAL INSTRUMENT CO., INC.

RED HOOK, N. Y.

Will Display in Booth 2 at the Clinical Congress

THE FOLLOWING INSTRUMENTS AND APPARATUS

Dooley Hip Pin Guide

**Bergamini Fracture and
Orthopedic Operating Frame**

Dooley Smith Peterson Hip Pin

Stephenson Impactor & Extractor

**Stephenson Universal & Kirschner
Wire Hand Drill**

Dooley Forearm & Leg Bone Spreader

Dooley Cast Wedge

**Kirschner Wire Traction & Tension
Retainer**

Kirschner Wires

THE HONOR OF YOUR PRESENCE WILL BE GREATLY APPRECIATED

Eisendrath & Rolnick—UROLOGY

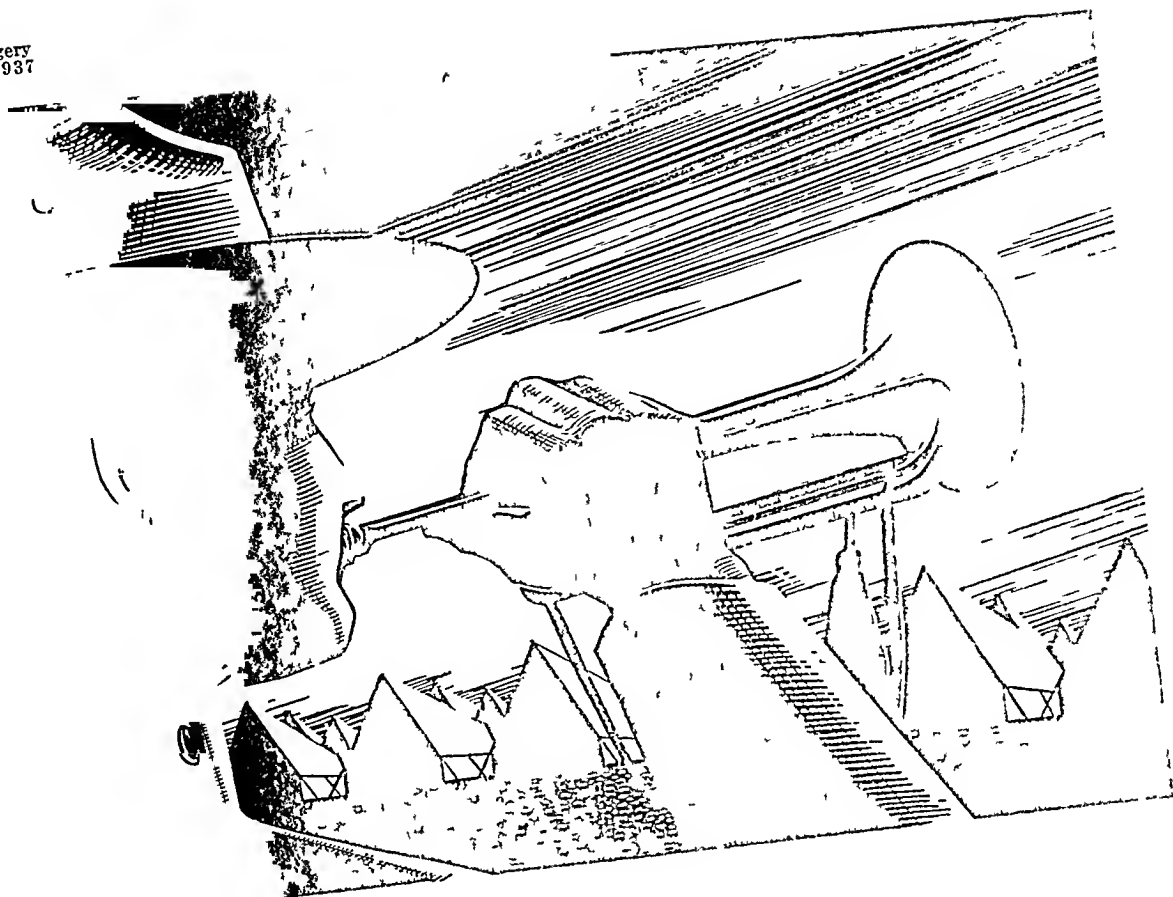
THIRD EDITION

This textbook on Urology presents the subject in the simplest possible manner. The rapid advances in this specialty during the past ten years have greatly broadened its field of application. The study of venereal diseases no longer constitutes the chief portion of the subject. The diagnosis and treatment of diseases of the urinary and genital tracts have attained a place of equal importance.

By DANIEL NATHAN EISENDRATH Consulting Urologist to the American Hospital Paris France, and HARRY CHARLES ROLNICK Clinical Professor of Genito Urinary Diseases Loyola University Medical School, Chicago Octavo 942 Pages 700 Illustrations 11 Colored Plates Cloth \$10.00

J. B. Lippincott Company

Philadelphia, Since 1792
London, Since 1875 Montreal, Since 1897



REGULATION

Regulation of the daily program, especially diet and exercise is beneficial, to normal bowel movement and in some cases of constipation serves as sufficient treatment. Others require additional aid to facilitate regular evacuation.

When an adjunct to diet and exercise is required, as it often is, Petrolagar provides a mild but effective

tive treatment. Its miscible properties make it easier to take and more effective than plain mineral oil. Further, by softening the feces Petrolagar induces large, well formed stools which are easy to evacuate. The five types of Petrolagar afford a choice of medication adaptable to the individual patient. Petrolagar Laboratories, Inc., Chicago



Petrolagar is a mechanical emulsion of pure liquid petrolatum (65% by volume) and agar-agar. Accepted by the Council on Pharmacy and Chemistry of the American Medical Association for the treatment of constipation.

Petrolagar

Please mention ANNALS OF SURGERY when writing advertisers

HARVARD MEDICAL SCHOOL COURSES FOR GRADUATES

GENERAL SURGERY

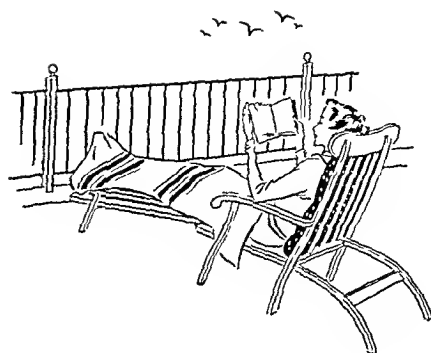
DECEMBER 1 31, inclusive,
at the BETH ISRAEL HOSPITAL

Ward rounds with emphasis on clinical diagnosis and pre- and post-operative management, exercises in history taking and the technic of physical diagnosis, conferences to consider the pathological physiology of the more important surgical diseases and to discuss the scientific basis for prevailing surgical procedures

FEE \$100 ATTENDANCE LIMITED

Apply to Assistant Dean,
Courses for Graduates,

HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS



CONVENIENT for CONVALESCENTS



At Chalfonte-Haddon Hall patients find many pleasures convenient to their quiet cheerful rooms Card rooms, game rooms and seaside lounges near the elevators Sunny Ocean Decks Modern health baths Squash courts Entertainments And dining-rooms where excellent food is served and where trained dietitians will supervise any special regimen you prescribe

October's the prime month by the sea Send your run-down patients down to build-up for winter Restricted clientele

LEEDS AND LIPPINCOTT COMPANY

CHALFONTE- HADDON HALL

ATLANTIC CITY



WANTED ANNALS OF SURGERY

April, May and
June, 1937
issues

*\$1.00 will be paid if in
good condition*

ANNALS OF SURGERY
227 South 6th Street
PHILADELPHIA, PA.



WISDOM is practical knowledge and it is acquired in the school of experience

First hand observation has taught physicians the world over that there is no better mineral oil emulsion than AGAROL. The wisdom of experience urges its use whether for the relief of acute constipation or for the treatment of habitual constipation. Effectiveness, palatability, convenience, every consideration favors Agarol.

The reasons why are briefly discussed in a folder, which we shall gladly send you with a liberal supply of Agarol. Please ask for it on your letterhead.



Agarol is available in 6, 10 and 16 ounce bottles.

AGAROL

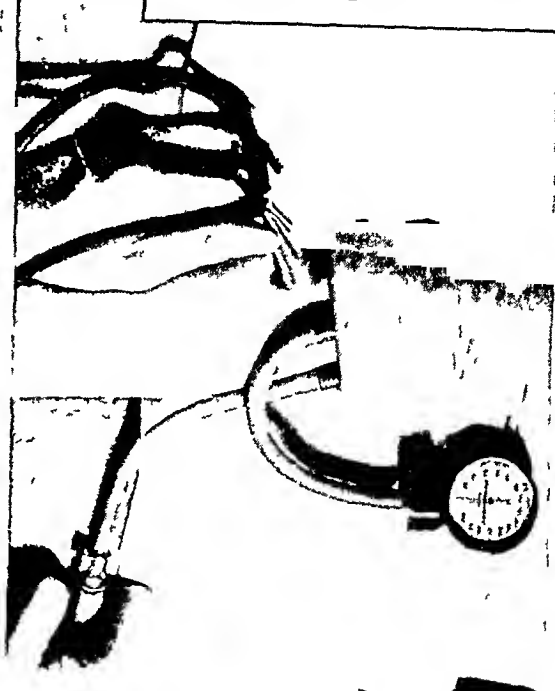
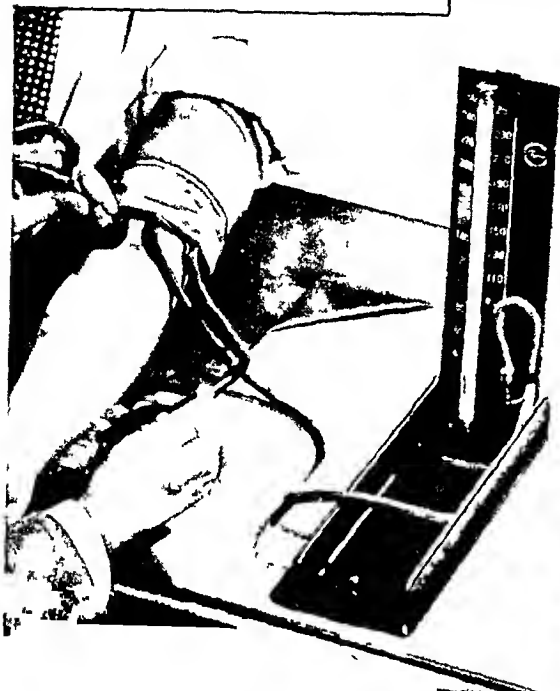
WILLIAM R. WARNER & COMPANY, INC.
113 West 18th Street New York City

Today in blood-pressure instruments

NEW *Tycos* MERCURIAL

It's Tycos

CERTIFIED *Tycos* ANEROID



WITH NEW AND EXCLUSIVE FEATURES AND UNLIMITED GUARANTEE OF ACCURACY

IF YOU like a mercury sphygmomanometer, here is one you will want to own. A professionally smart instrument you'll be proud to have on your desk or carry in your bag. Price \$27.50

CHECK THESE FEATURES OF THE TYCOS MERCURIAL
The only mercurial with a mercury lock to prevent leakage. A patented feature.

The only mercurial instrument case guaranteed against breaking.

The smallest mercurial made. Measures only $1\frac{3}{4}'' \times 3\frac{1}{2}'' \times 11\frac{1}{2}''$, yet reads to 260 mm.

Supported tube construction makes breakage of glass tube practically impossible.

New type of finish. Will not fingermark.

10 year guarantee against breakage or mechanical failure of the case.

10 year guarantee against breakage or mechanical failure of any part except inflation system. Includes free replacement of glass tube.

Unlimited time guarantee on accuracy under correct usage.

THE ACCURATE, DEPENDABLE INSTRUMENT WITH TEN-YEAR TRIPLE GUARANTEE

FOR the distinctive service this type instrument can give, more doctors today are using the Tycos Aneroid than ever before. Its long record of dependability, accuracy and durability has proved its value to thousands. Price \$25.00

THE CERTIFIED TYCOS ANEROID GIVES YOU—

Accuracy in any position. Upright, on its back or upside down, you can depend on it for a correct reading.

Automatic check on accuracy. As long as the pointer stays within the oval zero, it is guaranteed to be accurate. Never needs checking.

Super Portability. Compactness, lightness (only 16 oz.) and convenience in use.

Modern design. Rich black finish with chrome trim. Non-tarnishing dial, unbreakable crystal.

10 year triple guarantee. This iron clad guarantee is real protection. If the Tycos Aneroid is ever thrown out of adjustment, even due to fall, it will be corrected without charge for 10 years.

TYCOS EXCHANGE PLAN

On both the Mercurial and the Aneroid types your surgical supply dealer will allow you \$5.00 on the trade-in of your present sphygmomanometer—regardless of make or age.

TAYLOR INSTRUMENT COMPANIES ROCHESTER, NEW YORK

Makers of Taylor Pavaex and the noted Taylor-Tycos Clinical Thermometers

